Color Atlas
of
Hematology

Color Atlas of Hematology

WITH BRIEF CLINICAL DESCRIPTIONS
OF VARIOUS DISEASES

by
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For Medical Students Laboratory Technicians and General Practitioners of Medicine With Clinical and Hematologic Descriptions of Blood Diseases Including a Section on Terminology a Section on Technic and a Summary of Blood Findings in Various Diseases

Illustrated with 32 Plates in Full Color and 3 Plates in Black and White



Philadelphia London Montreal
J B LIPPINCOTT COMPANY

PRINTED IN THE UNITED STATES OF AMERICA

Preface

The preparation of this volume has been prompted by the belief that there is a widespread need for a color atlas of hematology particularly among medical students laboratory workers and general practitioners of medicine The various works hitherto available in this field have either originated in foreign countries or have been incomplete because of coverage of only certain phases of the subject.

All the color plates in this volume have been taken from my larger work Diseases of the Blood Although this volume is primarily a color atlas of blood diseases brief clinical descriptions of the various blood diseases have been incorporated These include descriptions of the anemias a discussion of the hemorrhagic syndromes and general treatment of the leukemias There will also be found a chapter on blood parasites including malarial parasites new material on the Rh factor and its clinical significance a chapter on definitions of hematologic terms a description of the origin of blood cells a chapter on the leukopenic syndromes and a chapter on miscellaneous blood diseases such as infectious mononucleosis polycythemia vera and Hodgkin s disease There is also a chapter on the splenomegalic diseases and splenectomy One section of importance particularly for technicians is a description of modern hematologic technical procedures One color plate is included also a description of blood of the various laboratory animals

The last section incorporates a summation of the hematologic findings in a wide variety of diseases and conditions

I hope that this volume will be of use to medical students laboratory technicians and general practitioners and that it will find a place in hospital and clinical laboratories of various types

Finally I wish to acknowledge the help received in the preparation of this work from my associate Dr William Riser Jr associate director of the Hematological Laboratory at the Medical College of Alabama, who prepared the section on Summary of Findings in the Various Diseases from Miss Helen Holt technical director of the Hematological Laboratory who prepared the section on Hematologic Technic and from Mrs Grace Thompson our efficient secretary who toiled over the manuscript

Roy R Kracke M D

Birmingham Alabama

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1

Definitions of Hematologic Terms

Absolute Increase of Cells

This term usually refers to an increase in one of the leukocyte-cell types. Thus with a count of 10 000 cells and 70 per cent neutrophils the absolute number of 7 000 neutrophils would be an absolute increase rather than a relative one

Achrestic Anemia

A macrocytic hyperchromic anemia with a blood picture identical with pernicious anemia except that it does not respond to treatment with antianemic factor presumably because of inability of marrow to utilize it.

Achromia

A condition in which the red cells are depleted of or without, hemoglobin Hypochromia is a better term

Acidocyte

Same as eosinophil acidophil eosinocyte

Addisonian Anemia

Same as pernicious anemia.

Agglutinogens A and B

The two agglutinogens found in the red cells of blood groups A B and AB

Agonal Leukocytosis

An increase in the total number of leukocytes in the blood just preceding death There is usually no shift in the differential count and all cell types are increased

Agranulocyte

A nongranular leukocyte or one without cytoplasmic granulation

Agranulocytosis (Malignant Neutropenia) (Essential Granulopenia)

A disease characterized by a deficiency of neutrophils in the blood In severe cases the lymphocytes and the monocytes also decrease in number

Aleukemic Leukemia (Aleukemic Myelosis) (Aleukemic Lymphadenosis)

The leukemic state characterized by leukopenia The total leukocyte count is decreased presumably because of leukemic-cell depositions in the various tissues

Amphophil

Referring to a granular leukocyte that has affinity for neither acid nor basic dyes The neutrophil of the rabbit

Anemia

A condition in which the blood is reduced in amount or is deficient in red blood cells or in hemoglobin A clinical term

Basophilia
(Basophilic Granulation)
(Diffuse Basophilia)

A condition in which basophils are increased in number

Biermer s Anemia

Same as pernicious anemia.

Blackwater Fever

A condition in which the urine of a febrile patient contains free hemoglobin in sufficient amount to color it dark or black

Bleeder

One who bleeds very easily Victim of hemophilia

Bleeding Time

Refers to the time that blood will drip from an ear or a finger puncture.

Blood Crisis

The appearance of large numbers *of nucleated red cells in the periph*eral blood frequently accompanied by reticulocytosis

Blood Dyscrasia

A disease of the blood or the blood forming organs

Blood Platelet

Same as thrombocyte

Bone Marrow Crisis

A condition which usually comes from the long standing destruction of red cells The bone marrow becomes functionally unable to produce cells the result being a shower of erythroblasts into the peripheral blood A sign of marrow erythropoietic exhaustion

Cabot s Ring

A ringlike or figure-of-eight basophilic structure found in some red cells in severe anemias

Capillary Resistance Test
(Rumpel Leede Test)

A test designed to determine the tendency of a patient to bleed in the skin A blood pressure cuff is placed round the arm and inflated to a point midway between the diastolic and the systolic pressures for five minutes after which the forearm is examined for petechiae

Chemotactic Factor

The hypothetical substance that is supposed to be responsible for attracting neutrophils from the bone marrow and also attracting them to sites of inflammation

Chloroleukemia

A leukemia like blood picture associated with marrow tumor growths of bright green color

Chloroma

Green tumor masses in the marrow not necessarily associated with a leukemic blood picture

Chlorosis (The Green Sickness)

A severe anemia of puberty in girls characterized by low hemoglobin and a low color index A classic example of iron-deficiency anemia

Clot Retraction Time

Refers to the length of time required for a blood clot to retract from the wall of a test tube in which the specimen is placed

Coagulation Time

Refers to the time required for blood to coagulate

Angina Agranulocytic

Same as malignant neutropenia

Anisocytosis

A condition in which the red cells are not uniform in size

Antianemic Factor

That substance which governs the orderly maturation of the red cells in the bone marrow especially at the megaloblastic level

Anticoagulant

A substance that prevents coagulation of blood Commonly used ones are potassium oxalate sodium oxalate heparin and many others

Aplasia

Incomplete or defective development A cessation of regeneration

Aplastic Anemia

A rare and fatal anemia of obscure etiology which is apparently the result of more or less complete failure of blood formation

Arneth Index

An index derived by computing the number of neutrophils into five classes depending on the number of nuclear lobes

Auto agglutinins

The presence of agglutinins that agglutinate the patient s own red cells at body temperature Cold agglutinins are those that agglutinate at lower temperatures

Ayerza s Disease

Polycythemia vera associated with stenosis of the pulmonary artery

Azurophilic Granules

Granules that stain well with red aniline dyes Small red granules that appear in the cytoplasm of lymphocytes

Band Forms

Neutrophils that show indentation of the nucleus in the early stage of nuclear lobulation

Banti s Disease

A syndrome characterized by splenomegaly hepatic cirrhosis hemorrhages from the upper gastro-intestinal tract and oftentimes a leukopenia

Basal Leukocyte Count

The number of leukocytes per cubic millimeter circulating in the blood at a time when the patient is resting under basal conditions

Basket Cell (Smudge Cell) (Degenerated Leukocyte)

A cell characterized by a network of fibrils irregular in shape and non nucleated thought to be an old degenerated leukocyte

Baso erythrocyte

A red cell showing the changes of basophilic degeneration including basophilic stippling punctate basophilia Cabot s ring bodies Howell Jolly bodies etc

Basophil (Basophile) (Basocyte)

A granular leukocyte having an affinity for basic stain in the cytoplasmic granules sometimes called mast cell

Erythremia (Polycythemia Vera)
A disease entity characterized by a marked increase in the number and the volume of the red blood cells, with cyanosis splenomegaly and usually hypertension

Erythroblast
A nucleated red blood cell including all nucleated types

Erythroblastemia
The presence of nucleated red cells in the peripheral blood

Erythroblastosis Foetalis
A condition of congenital generalized edema enlargement of liver and spleen jaundice and large numbers of erythroblasts in the blood A severe form of hemolytic anemia of the newborn

Erythrocyte
The red blood corpuscle The non nucleated hemoglobin-carrying corpuscle of the blood

Erythrocytometer (Hemocytometer)
An instrument for counting the red blood cells but sometimes used to designate an instrument to measure red cell diameters

Erythrocytopenia
Decreased numbers of red cells in the blood

Erythrocytosis
An increase in the number of red blood cells

Erythron
A term used to designate all the circulating red cells and the erythropoietic tissues from which they are derived

Erythropoiesis
The process of production of red blood cells in the bone marrow

Estivo autumnal Fever
The type of malarial infection caused by the parasite Plasmodium falciparum

Extrinsic Factor
That hypothetical dietary substance presumably protein in nature which unites with the gastric intrinsic factor to form the antianemia factor which governs orderly red-cell maturation

Fibrinogen
The precursor of fibrin in the blood clot

Filament Nonfilament Count
A differential count of the number of neutrophils showing nuclear division and those that do not show such division A divided nucleus is one that contains two or more lobes connected with slender strands of chromatic material known as filaments

Fragility Test
A test devised to determine the fragility of red cells by placing standard amounts of red cells in serial dilutions of hypotonic salt solution

Fragilocyte
A red cell that is unusually fragile when subjected to action by hypotonic salt solution as seen in the cells of congenital hemolytic icterus

Geisbock s Disease
Polycythemia vera associated with hypertension

Cold Agglutinins

A type of auto agglutinin that agglutinates the patient's own cells best at low temperature

Color Index

The ratio between the amount of hemoglobin and the number of red corpuscles It is obtained by dividing the per cent of red cells into the per cent of hemoglobin

Cooley's Anemia

An old term used to designate hemolytic anemia seen in children of Greek Italian and Sicilian parentage

Concentration of Leukocytes

The process of centrifuging a sample of the blood to which has been added an anticoagulant and removing the layer of concentrated leukocytes for study

Crenation

A mulberry like appearance of the red cells of the blood They are characterized by serrations on the surface of the affected cells Caused by cellular loss of fluid

Crenocyte

A red cell with serrated notched edges

Cross Matching of Blood

The technic of mixing donor's cells with recipient's serum and recipient cells with donor's serum to determine compatibility of the two bloods for purposes of transfusion

Cytopoiesis

Referring to the formation of cells

Degenerative Index

A *term* used to indicate the proportion of granulocytes that show toxic granules in the cytoplasm

Depressed Bone Marrow

A bone marrow with lowered cellular output or lessened functional activity

Digestive Leukocytosis

A term used to describe the leukocytosis that is supposed to occur after ingestion of food

Dorothy Reed Cells (Sternberg Cells)

The large multinucleated acidophilic giant cells seen in the tissues in Hodgkin's disease

Endothelial Leukocyte (Endotheliocyte) (Monocyte) (Transitional Cell)

The largest normal white cells characterized by variability in size large eccentrically placed nuclei with an abundant reticulated cytoplasm The nucleus may be lobulated deeply indented horseshoe shaped round or oval Cells arising from the reticulo-endothelial system

Eosinophil (Eosinophile) (Eosinocyte) (Eosinophilic Leukocyte)

A granular leukocyte in which the cytoplasmic granules stain readily with eosin and are large red shiny and refractile

Eosinophilia (Acidophilia) (Oxyphilia)

A relative leukocytosis in which the main increase is in the eosinophils

simple protein and hematin on hydrolysis

Hemoglobinemia

A condition in which the hemoglobin is dissolved out of the red cells and is in solution in the plasma Such blood is said to be laked

Hemoglobinometer

An instrument for estimating the amount of hemoglobin indicated in per cent of the normal or in grams per 100 cc of blood

Hemoglobinuria

The presence of hemoglobin in the urine To be distinguished from hematuria which is the presence of red cells in the urine

Hemogram

A systematic description of the findings in a blood examination

Hemolysis

Destruction of red cells by dissolution or lysis

Hemolytic Anemia

That type of anemia characterized by excessive intravascular destruction of red cells

Hemophilia

A hereditary disease characterized by prolonged coagulation of the blood and repeated hemorrhages occurring only in males and transmitted only by females and affected males

Hemorrhage Extravascular

The loss of blood from the vascular system into surrounding tissues into body cavities or externally

Hemorrhage Intravascular

The destruction of excessive numbers of red cells in the vascular system

Hemorrhagic Diathesis

A syndrome characterized by a tendency to spontaneous hemorrhages

Hemosiderosis

Infiltration of fixed tissues with the iron pigment hemosiderin which is derived from hemoglobin

Heterophil Antibody Test

A test performed by mixing normal sheep cells with serial dilutions of human serum followed in positive tests by agglutination of the cells Useful in diagnosing infectious mononucleosis

Hiatus Leukemicus

A term first used by Nageli to indicate a condition in which the blood shows extremely immature leukocytes with no intermediate forms the remainder being mature types Thought to be characteristic of leukemia

Histiocyte

Same as reticulo-endothelial cell

Histoplasmosis

An infectious disease caused by the organism Histoplasma capsulatum and characterized by enlarged liver spleen and lymph glands with a febrile course associated with leukopenia

Hodgkin s Disease

A systemic fatal disease of unknown etiology characterized by progressive lymph gland enlargement

Glandular Fever (Infectious Mononucleosis) (Benign Lymphadenosis)

A disease in which there is wide spread glandular enlargement associated with a relative and an absolute increase of atypical lymphocytes

Granuloblast

The precursor of a granulocyte

Granulocytes

White blood cells that contain cytoplasmic granules Include neutrophils eosinophils and basophils

Granulocytosis

The presence of increased numbers of granulocytes in the blood stream

Granulocytopenia

A decrease in the number of granulocytes in the blood stream

Granulopoietic

Pertaining to the tissue which takes part in the formation of granulocytes Under normal conditions this is located in the red marrow of the flat bones and in the epiphyses of the long bones

Halometer

An instrument designed for the purpose of estimating the average diameter of the red cells in a blood smear

Hem Hema Hemato Haem

Prefixes denoting blood

Hemocytometer (Hematometer) (Hemometer)

An instrument for counting the number of corpuscles in the blood

Hemagglutinin

An agent that causes agglutination or clumping of red blood cells

Hematoblast

The immature form of all blood cells

Hematocrit

A centrifuge for separating the solid elements of the blood from the plasma

Hematocyte

A term that includes all cellular elements in the blood including erythrocytes leukocytes and thrombocytes

Hematologist

One who makes a special study of the blood and the blood forming organs and is skilled in the technic of blood examinations and the diagnosis and the treatment of blood diseases

Hematology

The branch of medicine that has to do with the blood in all its relations A study of the blood and the blood forming organs

Hematopoiesis

The formation or production of blood cells

Hemoconia (Blood Dust)

Minute colorless highly refractive spheroidal shaped bodies constantly present in normal or pathologic blood Apparently they have no significance

Hemoglobin

The coloring matter of the red cells a conjugated protein yielding a

Leukemoid Reaction

A condition in which the granulopoietic tissue is subject to stimulation to the extent that large numbers of immature cells are found in the peripheral blood simulating leukemia

Leukoblast

The stem cell of all leukocytes

Leukocidin

A substance that i destructive to leukocytes such as some products of bacterial growth

Leukocyte

A white blood cell

Leukocytogenesis

Referring to the formation of leu *kocytes*

Leukocytosis

An increase in the number of circulating leukocytes

Leukon

A term that refers to all circulating leukocytes and the leukopoietic tissues from whi h they are derived Analogous to the erythron of the red cells and the thrombon of the blood platelets

Leukopenia

Referring to that condition in which there is a decreased number of circulating leukocytes

Leukopoiesis

Referring to the formation or production of leukocytes

Lymphatic Leukemia

A fatal disease characterized by neoplastic proliferation of the lymphoid tissues with generalized lymphadenopathy a high white-cell count and associated anemia

Lymphoblast

The immature form of the lymphocyte

Lymphoblastosis

The presence of lymphoblasts in the peripheral blood as seen in acute lymphatic leukemia

Lymphocyte

A rounded mononuclear cell derived from the lymphoid tissues usually classified into large and small *forms*

Lymphocytosis

An increase in the number of lymphocytes in the blood

Macroblast

A large erythroblast.

Macrocyte

A large red blood cell of any type with a diameter larger than normal

Macrocytic Anemia

An anemic state characterized by the presence of macrocytes in the blood

Macrocytosis

The presence of macrocytes in the blood

Macrophage

The large phagocytic cells derived from the reticulo-endothelial system

Malarial Parasite

The parasite transmitted by the mosquito to man whi h is responsible for the disease malaria

Howell Jolly Bodies

Small basophilic particles probably nuclear remnants sometimes seen inside red corpuscles

Hyperchromia

Referring to that state in which the red blood cells contain more than their normal amount of hemoglobin The color index is above one

Hypochromia

Referring to that condition in which the red cells contain less than their normal amount of hemoglobin Such cells show a central pallor and the color index is below one

Hypoplastic Anemia

Anemia resulting from bone marrow insufficiency or inability to produce sufficient numbers of red cells

Icterus Index

A term used to designate the amount of bilirubin in the blood plasma

Infectious Mononucleosis

See glandular fever A febrile disease characterized by generalized lymphadenopathy and by increased numbers of abnormal lymphocytes in the blood

International Classification of Blood Groups

A classification of the four blood groups based upon agglutinogen content of the red cells in which the four groups are classified as AB A B and O

Intrinsic Factor

That hypothetical substance presumably arising from the mucosa of the stomach which forms with the extrinsic factor to produce the anti anemia factor

Iron deficiency Anemia

Any anemia characterized by decreased amounts of hemoglobin in the red cells Such anemias are hypochromic

Jansky s Classification of Blood Groups

A classification of the four blood groups as 4 3 2 and 1 analogous to the International Groups AB A B and O

Juvenile Granulocyte

The same as a metamyelocyte A young neutrophil with indented nucleus that has not yet divided into two lobes

Lederer s Acute Hemolytic Anemia

A rapidly developing hemolytic anemia characterized by red-cell destruction reticulocytosis elevated icterus index and accompanied by a febrile reaction

Leukemia (Myelosis) (Lymphadenosis)

An ultimately fatal disease of the blood forming organs characterized by increased numbers of leukocytes and associated anemia

Leukemic Reticulo endotheliosis

A type of monocytic leukemia in which the cell proliferation is restricted to the reticulo-endothelial tissues

Monocyte (Large Mononuclear) (Endotheliocyte) (Transitional) (Endothelial Leukocyte)

A large mononuclear cell with pale blue cytoplasm containing a fine dust like granulation with a large irregular nucleus

Monocytic Leukemia

A type of leukemia in which the neoplastic proliferating cells are those giving rise to monocytes There are two types—leukemic reticulo-endotheliosis from the reticulo-endothelial system and monocytoid myelogenous leukemia from the bone marrow

Monocytosis

Increase in the number of monocytes in the peripheral blood

Mononuclear

Any cell that has a single nucleus Usually refers to the monocyte

Moss s Classification of Blood Groups

A classification of the four blood groups as 1 2 3 and 4 corresponding to Jansky s Groups 4 3 2 and 1 and International AB A B and O

Myeloblast

One of the large nongranular cells of the bone marrow which finally develops into a myelocyte and a granular leukocyte The nucleus contains from one to three nucleoli

Myeloblastemia

The presence of myeloblasts in the peripheral blood

Myeloblastic Leukemia

The type of leukemia characterized by the presence of myeloblasts in the blood

Myelocyte

The parent cell of granulocytes found in the bone marrow

Myelogenous Leukemia (Myeloid Leukemia) (Myelosis)

A fatal disease characterized by unrestrained proliferation of myeloid tissue and by increased numbers of mature and immature granulocytes in the blood with deposition of these cells in the various tissues and organs

Myeloid

Relating or pertaining to cells of the myelogenous series

Myelomatosis

The appearance of numerous myelomas in the myeloid cavity

Myelophthisis (Aplastic Anemia)

Atrophy and aplasia of all cellular elements in the bone marrow

Myelopoiesis

Term referring to formation of blood cells in the bone marrow

Neutropenia (Neutrocytopenia)

A deficiency in the number of neutrophils in the blood

Malignant Neutropenia

A clinical entity characterized by a marked decrease in the number of circulating white cells mainly neutrophils Caused by various drugs chemicals and toxins

Mast Cell

Same as a basophil

Maturation

The process of cells maturing to their adult forms

Maturation Factor

That substance which causes cells to come to maturity

Mean Corpuscular Hemoglobin

A term to express the amount of hemoglobin in the average red cell

Mean Corpuscular Hemoglobin Concentration

Refers to the per cent of hemoglobin in the average red cell

Mean Corpuscular Volume

Refers to the volume of the average red cell in a given blood sample.

Medulla

Refers to marrow The soft center of a part

Megakaryoblast

The precursor of the megakaryocyte

Megaloblast

A large nucleated red blood cell with a cart wheel and a reticular nucleus when stained A nucleated precursor of the normoblast

Megalocyte

An abnormally large red cell which is pathologic in origin

Meniscocyte (Sickle Cell)

A sickle or crescent shaped red cell, as seen in sickle cell anemia

Meniscocytosis (Sickle Cell Anemia)

The presence of meniscocytes in the blood

Metamyelocyte

A transitional form of granulocyte intermediate between the mature myelocyte and the two lobed granular leukocyte Called by Schilling the juvenile type of neutrophil

Microcyte

A red blood cell with a diameter smaller than normal

Microcytic Anemia

An anemia characterized by the presence of microcytes in the blood

Microcytosis

The presence of microcytes in the blood

Micromyeloblast

A small myeloblast sometimes the predominating cell in some cases of myeloblastic leukemia

Microspherocytosis

A state of the blood characterized by excessive numbers of red cells with small diameters but more globular than normal as seen in congenital hemolytic icterus

Monoblast

The parent cell of the monocyte.

Monocyte (Large Mononuclear) (Endotheliocyte) (Transitional) (Endothelial Leukocyte)

A large mononuclear cell with pale blue cytoplasm containing a fine dust like granulation with a large irregular nucleus

Monocytic Leukemia

A type of leukemia in which the neoplastic proliferating cells are those giving rise to monocytes There are two types—leukemic reticulo-endotheliosis from the reticulo-endothelial system and monocytoid myelogenous leukemia from the bone marrow

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A fatal disease characterized by unrestrained proliferation of myeloid tissue and by increased numbers of mature and immature granulocytes in the blood with deposition of these cells in the various tissues and organs

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Relating or pertaining to cells of the myelogenous series

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The appearance of numerous myelomas in the myeloid cavity

Myelophthisis (Aplastic Anemia)

Atrophy and aplasia of all cellular elements in the bone marrow

Myelopoiesis

Term referring to formation of blood cells in the bone marrow

Neutropenia (Neutrocytopenia)

A deficiency in the number of neutrophils in the blood

Neutrophil (Neutrocyte) (Polymorphonuclear) (Polymorph) (Polynuclear) (Polymorphonuclear leukocyte)

The white blood cell of bone marrow origin having a diffuse neutrophilic cytoplasmic granulation with nucleus segmented into two or more lobes

Neutrophilia

Referring to an increase in the number of neutrophils in the blood

Normoblast

The nucleated precursor of the normal erythrocyte

Normochromia

Refers to a normal hemoglobin content of red cells

Normocyte

A red blood cell of normal size

Oligemia

A state in which the total quantity of blood is diminished

Oligocythemia

The state in which there is a decreased number of all blood cellular elements

Osteosclerotic Anemia (Marble Bone Disease) (Osteosclerosis)

An anemia caused by proliferation of connective tissue or formation of solid bone encroaching on the marrow cavity

Ovalocyte

An oval shaped nonnucleated red blood cell

Ovalocytosis

A hereditary condition seen rarely in the human in which there are ovalocytes in the peripheral blood Ovalocytes are seen under normal conditions only in the camel

Oxalated Blood

Blood to which has been added one of the oxalate preparations to prevent its coagulation

Oxygen Tension

The amount of oxygen in the bone marrow which regulates the production of red blood cells

Pernicious Anemia

A classic type of hyperchromic, macrocytic anemia characterized by achylia gastrica various neurologic disorders and a fatal outcome unless treated by the antianemia factor in the form of liver extract

Peroxidase Reaction

A reaction obtained by treating blood cells with alphanaphthol and then with dimethylphenylenediamine Useful in differentiating granular leukocytes from the lymphoid series

Photelometer

An instrument designed to estimate the amount of hemoglobin by photo-electric methods

Plasma

The fluid part of the blood

Plasma Cell

A lymphocytic like cell with eccentrically placed deep staining nucleus appearing in wheel like fashion seen rarely in the peripheral blood

Plasmodium Falciparum

The parasite causing human malaria of the estivo-autumnal type

Plasmodium Malariae

The parasite causing human malaria of the quartan type

Plasmodium Vivax

The type of parasite causing human malaria of the tertian type.

Platelet

Same as thrombocyte

Plummer Vinson Syndrome

Difficulty in swallowing or dysphagia frequently associated with microcytic achlorhydric anemia

Poikilocyte

A red blood cell with an atypical shape The condition is referred to as poikilocytosis

Polycythemia

A state of the blood characterized by increased numbers of red cells

Polycythemia Hypertonica

Same as Geisbock s disease Polycythemia vera associated with hypertension

Polycythemia Vera

A clinical entity characterized by increased and sustained output of the bone marrow with respect to production of red cells Associated with splenomegaly hypertension and cyanosis

Polymorphonuclear Leukocyte

Same as neutrophil

Premyelocyte

The precursor of the myelocyte.

Price Jones Curve

A name applied to the curve derived by plotting the diameters of a large number of erythrocytes

Primary Anemia

An old hematologic term which referred mainly to pernicious anemia

Prothrombin

The inactive precursor of thrombin which is formed in the liver and depends upon adequate intake of vitamin K for its production

Pseudo-agglutination

Refers to rouleaux formation or stacking of red cells

Punctate Basophilia (Basophilic Stippling)

See basophilia

Purpura

The condition of bleeding into the skin or beneath the skin

Reticulocyte (Reticulated Erythrocyte)

A red blood cell showing a reticulum or network when stained with vital dyes The precursor of the normal red blood cell A stage between the nucleated red cell and the normal red cell

Reticulocytosis

The condition in which the normal number of reticulocytes (from 25 000 to 50 000 per cu mm) in the blood is exceeded

Reticulo-endothelial Cell

The cells which include Kupffer s cells in the liver the spleen the lymph glands and the bone marrow

Neutrophil (Neutrocyte) (Polymorphonuclear) (Polymorph) (Polynuclear) (Polymorphonuclear leukocyte)

The white blood cell of bone marrow origin having a diffuse neutrophilic cytoplasmic granulation with nucleus segmented into two or more lobes

Neutrophilia

Referring to an increase in the number of neutrophils in the blood

Normoblast

The nucleated precursor of the normal erythrocyte

Normochromia

Refers to a normal hemoglobin content of red cells

Normocyte

A red blood cell of normal size

Oligemia

A state in which the total quantity of blood is diminished

Oligocythemia

The state in which there is a decreased number of all blood cellular elements

Osteosclerotic Anemia (Marble Bone Disease) (Osteosclerosis)

An anemia caused by proliferation of connective tissue or formation of solid bone encroaching on the marrow cavity

Ovalocyte

An oval shaped nonnucleated red blood cell

Ovalocytosis

A hereditary condition seen rarely in the human in which there are ovalocytes in the peripheral blood Ovalocytes are seen under normal conditions only in the camel

Oxalated Blood

Blood to which has been added one of the oxalate preparations to prevent its coagulation

Oxygen Tension

The amount of oxygen in the bone marrow which regulates the production of red blood cells

Pernicious Anemia

A classic type of hyperchromic macrocytic anemia characterized by achylia gastrica various neurologic disorders and a fatal outcome unless treated by the antianemia factor in the form of liver extract

Peroxidase Reaction

A reaction obtained by treating blood cells with alphanaphthol and then with dimethylphenylenediamine Useful in differentiating granular leukocytes from the lymphoid series

Photelometer

An instrument designed to estimate the amount of hemoglobin by photo-electric methods

Plasma

The fluid part of the blood

Plasma Cell

A lymphocytic like cell with eccentrically placed deep staining nucleus appearing in wheel like fashion seen rarely in the peripheral blood

Plasmodium Falciparum

The parasite causing human malaria of the estivo-autumnal type

Plasmodium Malariae

The parasite causing human malaria of the quartan type

Plasmodium Vivax

The type of parasite causing human malaria of the tertian type

Platelet

Same as thrombocyte

Plummer Vinson Syndrome

Difficulty in swallowing or dysphagia frequently associated with microcytic achlorhydric anemia

Poikilocyte

A red blood cell with an atypical shape The condition is referred to as poikilocytosis

Polycythemia

A state of the blood characterized by increased numbers of red cells

Polycythemia Hypertonica

Same as Geisbock s disease Polycythemia vera associated with hypertension

Polycythemia Vera

A clinical entity characterized by increased and sustained output of the bone marrow with respect to production of red cells Associated with splenomegaly hypertension and cyanosis

Polymorphonuclear Leukocyte

Same as neutrophil

Premyelocyte

The precursor of the myelocyte.

Price Jones Curve

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Reticulo endothelial Cell

The cells which include Kupffer s cells in the liver the spleen the lymph glands and the bone marrow

Their chief function is phagocytosis of foreign material

Reticulo endothelial System

The system of cells that functions as a macrophage system

Rh Factor

A recently discovered factor or agglutinogen in the red blood cells of 85 per cent of humans making such cells susceptible to agglutination when brought in contact with anti Rh agglutinins

Rouleaux Formation

The stacked arrangement of red cells in the blood in which they appear as figures resembling stacks of coins

Schilling Index

A method of classifying neutrophils based on their age The neutrophils are counted and classified as myelocytes metamyelocytes (juvenile forms) band forms and segmented types

Secondary Anemia

An old hematologic term now abandoned which usually refers to hypochromic or iron-deficiency anemias

Sedimentation Rate

The rate at which red cells will fall in their own plasma in a given length of time

Serum

A clear straw-colored liquid which is that part of the blood plasma remaining after the blood has coagulated

Shift to the Left

A term used to designate that condition in which the immature forms of the neutrophils are increased above their normal number

Sickle Cell Anemia

A familial disease affecting Negroes chiefly and characterized by blood showing the presence of large numbers of sickle shaped red corpuscles (meniscocytes)

Sickling Trait

A condition seen chiefly in Negroes where a trait toward the sickling of red cells is observed yet not sufficient to cause clinical sickle cell anemia

Spherocyte

A red cell with a tendency toward a globular or rounded form The normal red cell is a *biconcave disk while* a spherocyte is more globular and biconvex with a smaller diameter

Spherocytic Anemia (Congenital Hemolytic Anemia)

An anemia characterized by the presence of large numbers of spherocytes

Splenectomy

Removal of the spleen

Splenic Anemia

Same as Banti s syndrome

Splenomegaly

Enlargement of the spleen from any cause

Stab Forms

A term synonymous with band forms as used in the Schilling classification of neutrophils.

Sternal Puncture

The process of puncturing the outer table of the sternum with a large needle and aspirating material from the sternal marrow for examination

Supravital Stain

Used to stain cells while they are still alive so that their vital and functional processes may be studied

Thromboblast

The precursor of the thrombocyte Same as megakaryocyte

Thrombocyte (Blood Platelet)

A circular or oval disk from one to three micra in diameter found in peripheral blood to the extent of about 300 000 per cu mm Formed in the bone marrow and important in the process of cessation of hemorrhage

Thrombocytopenia

A decrease in the number of blood platelets below normal

Thrombocytosis

An increase in the number of blood platelets above normal

Thrombon

A term used to designate all circulating thrombocytes and the tissues from which they arise

Thromboplastin

The substance that initiates the process of blood clotting

Thrombopoietic

Pertaining to the tissue which takes part in forming thrombocytes

Transitional Cell

Same as monocyte

Turk s Cell

An atypical form of lymphocyte characterized by a dark blue cytoplasm in the center of which is a characteristic nucleus Perhaps the same as a plasma cell

Urobilinogen

The end product of red-cell destruction which is found in the urine in increased amounts in patients with hemolytic anemia

van den Bergh s Reaction

Designed to distinguish between two types of bilirubin in blood plasma

Venepuncture

The act of puncturing a vein in order to remove a sample of blood

Vitamin K

A vitamin of normal diet requiring bile salts for activation which finally is converted by the liver into prothrombin The precursor of prothrombin

Volume Index

A term used to designate the volume of the packed cells as compared with the normal

Volume of Packed Cells

Refers to the relative volume occupied by the blood cells after they have been packed to the bottom of a tube with high speed centrifugation (In men 45 per cent in women 42 per cent of the total blood volume)

von Jaksch s Anemia

An anemia of childhood characterized by leukocytosis and large numbers of normoblasts with reticulocytosis It is a typical erythroblastic hemolytic anemia

Their chief function is phagocytosis of foreign material

Reticulo endothelial System

The system of cells that functions as a macrophage system

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Enlargement of the spleen from any cause

Stab Forms

A term synonymous with band forms as used in the Schilling classification of neutrophils

lakes that have a low oxygen content which is the single most important factor in stimulation of production of erythrocytes On the other hand production of granulocytes seems greatest when there is dilation of sinusoids In general low oxygen tension and high temperature stimulate production of red cells

The earliest recognizable red cell in the bone marrow is the megaloblast This develops into a macroblast and then into a normoblast which is a normal sized nucleated red cell After solution or disappearance of the nucleus it is converted into the reticulocyte which after losing its reticulum is discharged into the peripheral blood as a normal erythrocyte

The granular leukocytes including neutrophils eosinophils and basophils arise from a single stem cell the earliest recognizable form being the myeloblast and after the cytoplasm becomes faintly granulated the cell becomes a premyelocyte At this point it shows the first evidence of differentiation into the three types of myelocytes The myelocyte develops into the metamyelocyte or so-called juvenile form with further development its nucleus becomes band shaped and it is referred to as a band and just beyond this stage after slight segmentation of the nucleus it is released into the peripheral circulation (see Plate 6)

There is also found in the bone marrow a considerable number of large multinucleated cells known as megakaryocytes which have a light blue highly granulated cytoplasm small portions of which become pinched off and escape into the blood where they then become known as thrombocytes or blood platelets

Lymphocytes are derived from the widespread lymphoid tissue the earliest recognizable cell being the lymphoblast which develops first into the large form of lymphocyte and finally into the small lymphocyte as the most adult type

Monocytes apparently have their origin from the widespread reticulo endothelial elements the earliest recognizable cell being the monoblast this in turn becoming the fully developed monocyte as seen in the peripheral blood

It is important for the clinical hematologist to remember always that all granulocytes erythrocytes and thrombocytes are formed in the red marrow that lymphocytes arise from lymphoid tissue and that monocytes arise from reticulo-endothelium This basic concept offers the most satisfactory working basis for the solution of practical hematologic problems For a study of the cytologic pattern of the bone marrow and methods for its removal and study see Chapter 17

2

Origin and Development of Blood Cells

(See Plate 1 pp 18 19)

Although there has been considerable controversy with regard to the origin of blood cells this has centered in the problem as to whether all cells arise from a single polyvalent cell known as the hematocytoblast or whether there are two or perhaps three cells of origin The former concept is usually referred to as the monophyletic theory and the latter as the polyphyletic theory In any event there is general agreement that erythrocytes granulocytes and thrombocytes arise from tissue of the bone marrow that the lymphocytes arise from the generalized lymphoid tissue and that the monocytes have their origin from reticulo-endothelium whatever its location

THE BONE MARROW

The bone marrow is the largest organ in the body consisting of nearly 5 per cent of the total body weight All together it weighs nearly 4 000 grams almost twice as much as the liver It is a widespread organ located in many anatomic sites The active red cell producing marrow is found in the flat bones such as sternum ribs vertebrae skull and pelvis in addition to the epiphyseal ends of the long bones Therefore the marrow produces blood cells in literally hundreds of different locations

At birth all the marrow is red and active but during childhood there is gradual fat replacement in the diaphysis of the long bones Later in life this yellow marrow can become active again if more blood cells should be required The marrow therefore has a great reserve power for the production of blood cells should the time ever come when greater than normal production is necessary

Yellow bone marrow consists simply of masses of round fat cells supported in fine strands of connective tissue In such marrow there is a very small amount of potential hematopoietic elements Active red marrow consists of a network of intercommunicating but large vessels which are lined with endothelium and are known as sinusoids This results in a vascular system that is of the closed type In this marrow pattern the erythrocytes are produced intravascularly the leukocytes extravascularly The blood flow through the marrow is extremely sluggish since the blood flows very slowly forming pools and

PLATE 1

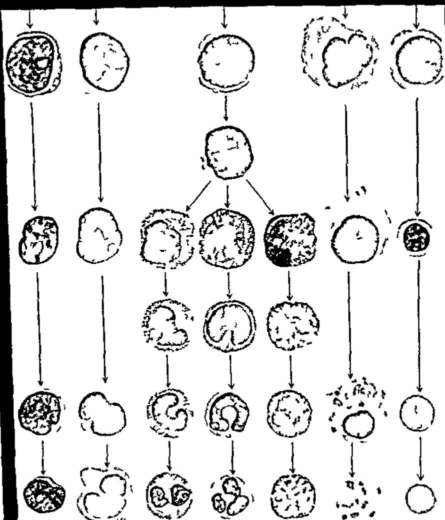
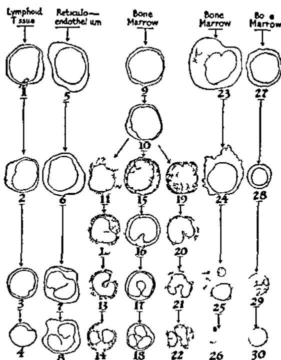


PLATE 1

ORIGIN AND DEVELOPMENT OF BLOOD CELLS



1 Lymphoblast
2 Large lymphocyte
3 Intermediate lymphocyte
4 Small lymphocyte
5 Monoblast
6 Large monocyte with azure granules
7 *Monocyte with a few granules*
8 Mature monocyte with azure granules
9 Myeloblast
10 Premyelocyte
11 *Eosinophilic myelocyte*
12 Juvenile eosinophil
13 Band eosinophil
14 Segmented eosinophil
15 Neutrophilic myelocyte
16 Juvenile neutrophil
17 Band neutrophil
18 Segmented neutrophil
19 Basophilic myelocyte
20 Juvenile basophil
21 *Band basophil*
22 Segmented basophil
23 *Megakaryocyte (bone marrow)*
24 Later megakaryocyte (bone marrow)
25 Megakaryocyte (peripheral blood)
26 Thrombocytes (platelets)
27 Megaloblast
28 Normoblast
29 Reticulocyte
30 *Normocyte (erythrocyte)*

BAND OR STAB NEUTROPHIL

In this cell the differentiation has proceeded to the point where the nucleus becomes a curved or irregular shaped band This is just prior to its division into lobes Cytoplasmic granulation has become similar to that seen in the adult form

SEGMENTED NEUTROPHIL

When nuclear segmentation occurs the cell is then considered to be a young adult and is ready for delivery into the blood stream The lobes vary from two to five and are connected by a single fine chromatin strand Neutrophilic granulation is dispersed throughout the cytoplasm

EOSINOPHILIC MYELOCYTE

This type of cell is similar to the neutrophilic myelocyte except that the cytoplasm contains many large coarse orange red granules which are scattered over both cytoplasm and nucleus Sometimes they appear bronze or dirty yellow because of some slight basophilic tint The cell then develops through the typical stages of maturation to the fully segmented adult eosinophil

BASOPHILIC MYELOCYTE

This cell is similar to the neutrophilic myelocyte except that it appears to be smaller with a diameter of from 10 to 12 micra only as compared with from 15 to 18 micra for the neutrophilic form It develops in the usual pattern of maturation until complete nuclear segmentation has occurred with the cytoplasmic granulation being dark blue or dark purple and the granules frequently so numerous that the nuclear outlines are obscure The basophilic myelocyte is seldom seen in the peripheral blood except in cases of leukemia and when they occur in leukemia in large numbers it is thought to be a bad prognostic sign The function of the basophil is not known but it is not seen in response to infectious diseases Some believe that the basophilic granules may be the source of heparin In contrast with neutrophils and eosinophils this cell is not seen in fixed tissues in histologic sections since the granules are water soluble

LYMPHOBLAST

The lymphoblast is a large mononuclear cell which cannot be distinguished with certainty from the myeloblast except that the nuclear chromatin is coarser and less homogeneous and the number of nucleoli usually range from one to three in contrast with from three to five in the myeloblast There is usually a clear perinuclear zone which is not found in the typical myeloblast These cells are seen in large numbers in acute lymphatic leukemia occasionally in chronic lymphatic leukemia and rarely in other conditions such as acute infectious mononucleosis

YOUNG LYMPHOCYTE

As the lymphoblast develops its next phase is that designated as the young lymphocyte in which the cell is still fairly large with the nuclear chromatin less dense than in the mature form The sky blue cytoplasm shows a perinuclear pallor and it may contain a few scattered bright red granules which are known as azure granules

3

Morphology of Blood Cells

(See Plates 2 and 3 pp 22 25)

MYELOBLAST

All granulocytes arise from the parent stem cell, the myeloblast, which is the earliest recognizable precursor seen in the bone marrow The myeloblast is usually an extremely large cell It does not have granules in its cytoplasm and bears a close resemblance to other leukoblasts particularly the lymphoblast When stained with polychrome dyes such as Wright s stain the nucleus is reddish purple in color and usually round but occasionally oval in shape The nucleus contains from three to five nucleoli and is quite homogeneous in comparison with that of the lymphoblast There is no definite nuclear membrane The cytoplasm is usually light blue without the perinuclear zone It cannot be identified by the use of peroxidase stains When large numbers of myeloblasts are seen as in leukemia other more mature forms are usually seen and aid in its identification For the different types of myeloblasts see Plate 4

PREMYELOCYTE

The morphology of this cell is similar to the myeloblast except that the nucleoli are less distinct and there are a few cytoplasmic granules Because of the granulation it is possible at this point to determine what type of granulocytic cell it will eventually become

NEUTROPHILIC MYELOCYTE

This stage of development is characterized by large numbers of neutrophilic granules which are scattered throughout the cytoplasm and appear to cover the nucleus as well The granules are wine-colored and sometimes appear to be a mixture of blue and *red*

NEUTROPHILIC METAMYELOCYTE (JUVENILE NEUTROPHIL)

In this cell the differentiation is more advanced the nucleus has become slightly indented or even horseshoe shaped and shows a sharp nuclear membrane The chromatin material is more dense than in the myelocyte and the nucleoli have completely disappeared The granules are very small and stain a lavender pink This cell normally does not appear in the peripheral blood but is found there only under conditions of intense marrow stimulation







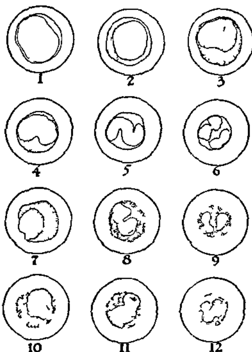







PLATE 2

MORPHOLOGY OF BLOOD CELLS
(GRANULOCYTES)



1 Myeloblast	7 Eosinophilic myelocyte
2 Premyelocyte	8 Juvenile eosinophil
3 Neutrophilic myelocyte	9 Segmented eosinophil
4 Juvenile neutrophil	10 Basophilic myelocyte
5 Band neutrophil	11 Juvenile basophil
6 Segmented neutrophil	12 Segmented basophil

Cells drawn on large scale to show particularly the individual cellular morphology of the typical cell For variations in morphology see other plates

PLATE 3

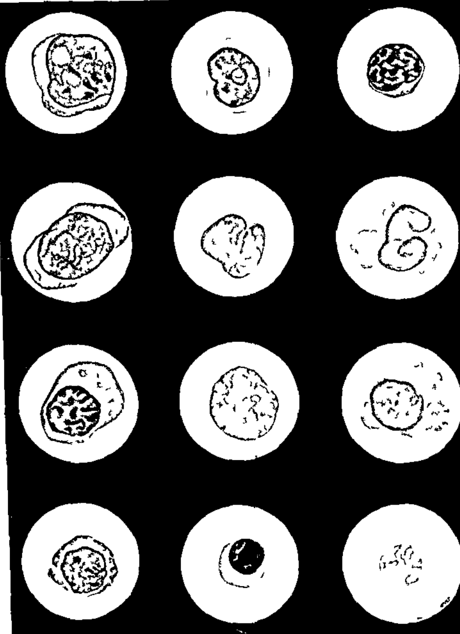
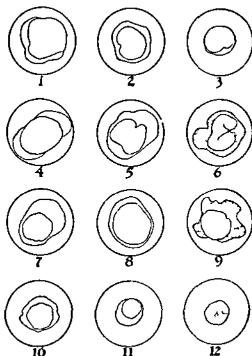


PLATE 3

MORPHOLOGY OF BLOOD CELLS
(LYMPHOCYTES MONOCYTES ERYTHROCYTES)



1 Lymphoblast
2 Large lymphocyte without azure granules
3 Small lymphocyte
4 Monoblast
5 Immature nongranular monocyte
6 Mature granular monocyte
7 Plasma cell
8 Primitive cell (stem cell)
9 Megakaryocyte
10 Megaloblast
11 Normoblast
12 Reticulocyte

fine azure granules Small portions of this cytoplasm are thought to become broken off and flow into the peripheral blood as blood platelets or thrombocytes Some megakaryocytes show multiple nuclei giving a cytologic appearance similar to Dorothy Reed giant cells

MEGALOBLAST

The megaloblast is the largest known recognizable precursor of the normal red cell It is frequently difficult to distinguish from some types of myeloblasts The chromatin arrangement in the nucleus is similar to that of the myeloblast but the cell is usually smaller Another feature is the distinctness of the nuclear membrane The cytoplasm is grayish blue in color and frequently irregular in outline Megaloblasts are found in the peripheral blood in those conditions in which there is an arrest of maturation at the megaloblastic level in the bone marrow as seen in pernicious anemia and other similar macrocytic anemias

NORMOBLAST

The normoblast is the next stage in the development of the red cell This nucleated red cell is usually of normal size from seven to nine micra in diameter and the small round deep purple staining nucleus may be seen either in the center or near the periphery of the cell The cytoplasm is blue pink in color and even before the nucleus is lost the cytoplasm becomes pink because of hemoglobinization of the cell

RETICULOCYTE

The reticulocyte is thought to be the intermediate stage between the nucleated and the nonnucleated forms of the erythrocyte When stained with vital dyes such as brilliant cresyl blue it is characterized by the presence of a fine skeinlike reticulum which however cannot be seen when stained by ordinary staining methods (See page 160 for technic for reticulocyte counts) Reticulocytes comprise normally from ½ to 1 per cent of the erythrocytes in the circulating blood The presence of increased reticulocytes in peripheral blood always means a very active bone marrow so far as erythropoiesis is concerned Large numbers of them are seen especially in cases of active bone marrow regeneration in various hemolytic anemias and in instances of cell regeneration during active treatment of macrocytic anemias

MATURE LYMPHOCYTE

This cell which varies in size from 7 to 12 micra in diameter, shows the nucleus to have a greater affinity for basic dyes than the more immature types It is usually small round in shape the nucleus frequently in dented and in many of them the cy toplasm is so reduced in amount that it occurs only as a small thin rim

MONOBLAST

This is a very large mononuclear cell sometimes as much as 25 micra in diameter It has a large purple red nucleus and deep blue cytoplasm and cannot be distinguished with cer tainty from the myeloblast and the lymphoblast Its recognition is based frequently on its association with other types of monocytes

NONGRANULAR MONOCYTE

This is the intermediate stage be tween the monoblast and the fully developed granulated monocyte The nucleus is pale lavender and shows much finely woven chromatin reticu lum The nucleus is indented con voluted often eccentric in position and frequently gives an impression of overfolding The cytoplasm is a cloudy blue color

MATURE MONOCYTE

The mature monocy e remains as large as its younger form in many cases but it may be smaller The nu cleus is characterized by a marked indentation and convolutions and is sometimes horseshoe shaped this giv ing rise to the older designation of transitional cell The light blue cyto plasm is filled with small azurophilic granules that are finer than those of the large lymphocyte and pinker than those of the neutrophil The cyto plasm may show irregular extrusions of various types such as those of an ameba This cell is frequently con fused with the juvenile type of neu trophil

PLASMA CELL

The characteristic plasma cell is a large one with an intense violet blue color The nucleus which is typically eccentric in position usually is round and sometimes appears to be almost extruding from the cytoplasm The chromatin material is coarse and has an arrangement which suggests the spokes of a wheel The perinuclear zone is quite pronounced The cyto plasm is dark blue and frequently contains vacuoles The plasma cell is probably a form of lymphocytic cell and no doubt has its origin from the lymphoid tissue

THE PRIMITIVE CELL

This large cell may be an atypical type of the various blast forms It has a very loosely woven pale laven der nucleus and a pale halo-blue cyto plasm Such cells are seen only in rare instances of the acute forms of leu kemia

MEGAKARYOCYTE

This extremely large cell which is the largest one seen in the blood or bone marrow is the precursor of blood platelets It is quite irregular has a lavender nucleus and a pale blue cytoplasm which contains many

cells of the more mature granulocytic types such as an occasional premyelocyte or myelocyte that indicates the nature of the blast cell in question which bears out the old adage that sometimes a cell can be identified only by the company it keeps

Myeloblasts are never seen in the peripheral blood under normal conditions and even in severe infectious diseases with the most intense marrow stimulation it is rare to see a cell as immature as the myeloblast They are found in large numbers in the spleen and the liver during embryonic life and for some time after birth comprise the greater part of the marrow cells They seem to be more numerous in the marrow of children than adults The finding of an occasional myeloblast in the peripheral blood of a child does not have the same grave prognostic import as does the finding of the same cell in the blood of an adult

In some cases of myeloblastic leukemia the peripheral blood pattern may consist mainly of numbers of myeloblasts and mature forms of granulocytes without any intermediate forms between the two This situation appears to be brought about by a rather sudden inability of the leukemic bone marrow to produce mature granulocytes with a coincidental cessation of cell maturation on the myeloblastic level This is known as hiatus leukemicus and is said by Nageli to be pathognomonic of the leukemic state

MYELOCYTES

(See Plate 5 pp 32 33)

In the maturation of granulocytic leukocytes the myelocytes and the premyelocytes represent intermediate stages between the myeloblasts and the mature functioning granulocytes Cells 1 to 3 in Plate 5 show the various types of premyelocytes that may be found in normal bone marrow and occasionally in the peripheral blood in response to stimulation by infectious disease These cells differ little from myeloblasts in their nuclear framework and cytoplasmic color, but the cytoplasm contains a few scattered wine red granules The premyelocyte has the potentiality of developing into any one of the three myelocytes that is the neutrophilic the eosinophilic and the basophilic types Cells 4 to 12 vary in details of cytoplasmic color distinctness of nuclear outline and size of granules in the nucleus but all have the common characteristic of having wine-colored or lavender granulation scattered densely throughout the cytoplasm and as a rule over the surface of the nucleus sometimes to such an extent that the nuclear outlines can barely be determined The granules are neither basic blue nor eosin red in color but are thought to be a combination of the two

The three eosinophilic myelocytes shown in this plate are characterized by indistinctness of the nucleus a rather light basic color of the nucleus and the presence of large numbers of red and orange colored granules Sometimes eosinophilic granules are so closely packed into the cell that the entire cell appears to be bronze in color Cells 16 to 18 are basophilic myelocytes in which there are variable numbers of dark

4

Myeloblasts and Myelocytes

MYELOBLASTS

(See Plate 4 pp 30 31)

Many different types of myeloblasts are shown on Plate 4 because it is important that the student recognize the various atypical forms in which this cell may occur Since myeloblasts are so frequently confused with lymphocytes by students and technicians the result is that many cases of myeloblastic leukemia go un recognized particularly if the blood is studied in the aleukemic phase Myeloblasts are found in considerable numbers under normal conditions in the bone marrow where they undergo a definite maturation pattern into the granulocytic cells but in leukemia this pattern becomes atypical and disorganized resulting in many morphologic deviations from the normal

A typical myeloblast is a cell that that has a round or an oval nucleus with a finely woven nuclear network showing from three to five nucleoli without basichromatin clumping at the edges *It has no definite nuclear* membrane and usually has a sky blue cytoplasm without a light perinuclear halo In contrast the lymphoblast has coarser chromatin and fewer nucleoli a marked nuclear membrane and a distinctive perinuclear pallor The myeloblasts shown on Plate 4 were drawn from various cases of acute myeloblastic leukemia and were chosen to show some common atypical variations from the normal The first six cells can be classified as macromyeloblasts because of their size One of them shows distinct Auer bodies in the cytoplasm Another shows apparent protrusion of the cytoplasm Still another shows a fairly common type of atypical cell division which may be seen in the cells in the peripheral blood Cells 7 to 9 are myeloblasts of approximately normal size and can be designated as normomyeloblasts Cell 9 is a myeloblast with a fairly typical nucleus but the neutrophilic cytoplasm has matured apparently beyond the myeloblast stage Such disordered types of maturation are seen frequently in various forms of myeloblastic leukemia The last six cells are micromyeloblasts and it is this type of cell that so often resembles the lymphocyte in size and in staining properties and because of this becomes a difficult diagnostic problem for the inexperienced student or laboratory technician *When* they are present in large numbers they may give the false impression of chronic lymphatic leukemia Peroxidase stains will not aid in identifying these cells In many cases of acute myeloblastic leukemia a sign of considerable value is the finding of other

cells of the more mature granulocytic types such as an occasional premyelocyte or myelocyte that indicates the nature of the blast cell in question which bears out the old adage that sometimes a cell can be identified only by the company it keeps

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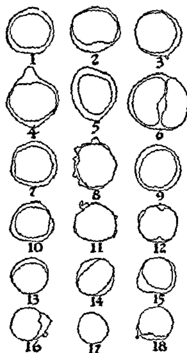
(See Plate 5 pp 32 33)

In the maturation of granulocytic leukocytes the myelocytes and the premyelocytes represent intermediate stages between the myeloblasts and the mature functioning granulocytes Cells 1 to 3 in Plate 5 show the various types of premyelocytes that may be found in normal bone marrow and occasionally in the peripheral blood in response to stimulation by infectious disease These cells differ little from myeloblasts in their nuclear framework and cytoplasmic color but the cytoplasm contains a few scattered wine red granules The premyelocyte has the potentiality of developing into any one of the three myelocytes that is the neutrophilic the eosinophilic and the basophilic types Cells 4 to 12 vary in details of cytoplasmic color distinctness of nuclear outline and size of granules in the nucleus but all have the common characteristic of having wine-colored or lavender granulation scattered densely throughout the cytoplasm and as a rule over the surface of the nucleus sometimes to such an extent that the nuclear outlines can barely be determined The granules are neither basic blue nor eosin red in color but are thought to be a combination of the two

The three eosinophilic myelocytes shown in this plate are characterized by indistinctness of the nucleus a rather light basic color of the nucleus and the presence of large numbers of red and orange-colored granules Sometimes eosinophilic granules are so closely packed into the cell that the entire cell appears to be bronze in color Cells 16 to 18 are basophilic myelocytes in which there are variable numbers of dark

PLATE 4

MYELOBLASTS



1 Macromyeloblast with round nucleus and sky blue cytoplasm
2 Macromyeloblast with oval nucleus and Auer bodies in the cytoplasm
3 Macromyeloblast with intense blue cytoplasm
4 Macromyeloblast with irregular nucleus and protrusion of cytoplasm
5 Macromyeloblast with vacuoles in a deeply staining cytoplasm
6 Macromyeloblast in division
7 Normomyeloblast
8 Normomyeloblast with numerous irregular protrusions of cytoplasm
9 Normomyeloblast in which the cytoplasm stains more acidophilic than normal but the nucleus has not developed
10 Normomyeloblast with a perinuclear area of azurophilic progranulation
11 Normomyeloblast with a large nucleus and only a remnant of cytoplasm
12 Normomyeloblast with atypical lobulation of nucleus
13 14 and 15 Micromyeloblasts corresponding in size to intermediate lymphocytes
16 17 and 18 Micromyeloblasts corresponding in size to small lymphocytes (Cell 17 has no cytoplasm)

PLATE 4

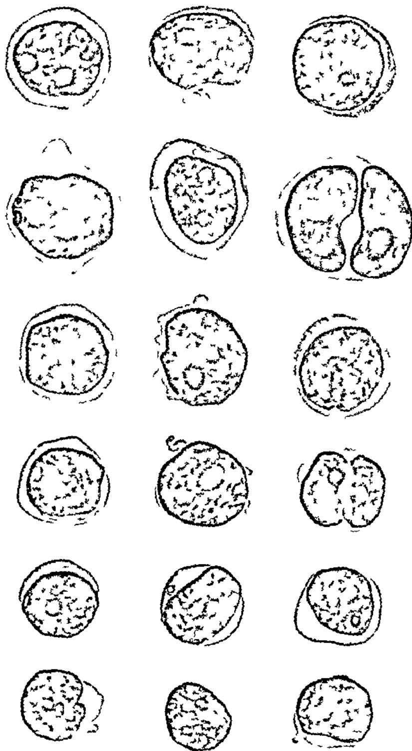
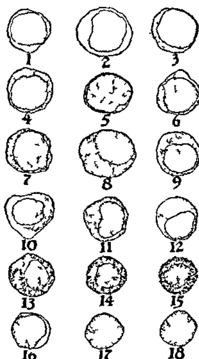


PLATE 5

MYELOCYTES



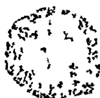
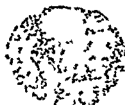
1 Premyelocyte with scanty granulation and centrally placed nucleus
2 Large premyelocyte
3 Premyelocyte with eccentric nucleus
4 5 6 7 8 and 9 Early neutrophilic myelocytes with blue cytoplasm and brilliantly stained granules (Myelocyte C of Sabin)
10 11 and 12 Late neutrophilic myelocytes with more delicately stained granules and cytoplasm (Myelocyte C of Sabin)
13 Early eosinophilic myelocyte with dark bronze granules and blue cytoplasm
14 and 15 Late eosinophilic myelocytes with numerous brilliant granules
16 Early basophilic myelocyte with blue cytoplasm and only a few granules
17 and 18 Late basophilic myelocytes with numerous granules and indistinct nuclear outlines

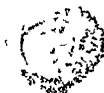
PLATE 5

















blue-colored granules arranged in the same way as those in the eosinophilic types

Neutrophilic myelocytes comprise the largest number of myelocytic cells seen in normal bone marrow Under normal conditions they are never seen in peripheral blood However myelocytes in small numbers may be seen *in peripheral blood only during severe* bone marrow stimulation particularly in the leukemoid reactions

Chronic myelogenous leukemia is the only condition in which one is likely to find all three types of myelocytes present in the peripheral blood In rare instances of eosinophilia the bone marrow reaction may be so marked that there may occur immature eosinophils which are difficult to distinguish from eosinophilic myelocytes Rare cases of chronic myelogenous leukemia may be characterized by large numbers of eosinophilic or basophilic myelocytes in which case the condition is designated as eosinophilic or basophilic myelogenous leukemia

DEVELOPMENT OF A MYELOCYTE AND CLASSIFICATION OF NEUTROPHILS

(See Plate 6 pp 36 37)

This plate is designed to show the development of a myelocyte through its various stages into a fully seg*mented and then hypersegmented* neutrophil It also shows the various types of cells that may evolve in this process which should aid the student in placing these cells in the various classifications that have been devised to record degrees of cell immaturity The classifications most widely used are those of Schilling Arneth Pons and Krumbhaar Cooke and Ponder, and the filament and the nonfilament count All these classifications have the same purpose in view that is to devise a system whereby cellular immaturity may be recorded and tabulated The Schilling classification is preferred by most laboratory workers

As the myelocyte develops as seen in cells 1 to 3 the development reaches the point where indentation of the nucleus becomes sufficient to classify the cell as a metamyelocyte or in the Schilling classification as a juvenile cell As nuclear indentation pro*gresses and cytoplasmic granulation* becomes less marked the cell then becomes known as a band a stab or a staff form in Schilling s classification Such cells are seen in Nos 10 to 12 Cell 12 shows the nucleus apparently extending in length and even though still band shaped it has assumed an S like form This stage is usually that preceding segmentation of the nucleus As development proceeds as seen in cell 13 the nucleus becomes divided into two or more lobes and the cell is then known as a segmented neutrophil sometimes called a segmenter All cells subsequent to that period of development are of course segmented types It is only at the stage of segmentation that the cell is released into the peripheral blood

The last six cells shown on this plate are those ordinarily found in normal blood The neutrophil after release from the bone marrow functions for a period of from four to six days before it becomes fully segmented and ready for removal from

the blood stream It is thought that some patients with pernicious anemia show an unusual number of neutrophils in which there is a great increase in the number of lobes This is called nuclear hypersegmentation as seen in cells 16 to 18 In general, hypersegmentation probably has no diagnostic significance

The Schilling classification divides these cells into myelocytes, juvenile forms, bands and segmented types As shown in this plate cells 1 to 3 are myelocytes cells 4 to 6 are juvenile types, cells 7 to 9 are probably juveniles with cell 9 possibly being a band, and cells 13 to 18 are segmenters Pons and Krumbhaar have suggested a classification based on the number of filaments between the segmented lobes of the nucleus According to their classification, cells 1 through 12 are nonfilamented cells and cells 13 through 18 are filamented Cooke and Ponder s classification is based upon the number of lobes in the nucleus, and according to this cells 1 through 12 show one lobe cell 13 shows two lobes, cells 14 and 15 show four lobes cell 16 shows five or six lobes, and cells 17 and 18 show seven lobes Arneth s classification attempts the same thing by designating all single lobe nuclei as class 1 and then dividing all segmented cells into classes 2, 3 4 and 5 depending upon the number of lobes in the nucleus. The Schilling classification is much superior to the others since it designates in the most accurate way the exact stage of development in the process of maturation The Schilling classification applied to normal blood shows all circulating neutrophils to be segmented types, with the exception of from 3 to 4 per cent of band forms.

When the bone marrow is subject to intense stimulation as seen in many infectious diseases larger numbers of the more immature forms appear These include considerable numbers of bands and juveniles, and occasionally even myelocytes This shift toward immaturity is generally referred to as a shift to the left, and is thought to be characteristic of all conditions in which the bone marrow is subject to stimulation with regard to its granulopoietic elements

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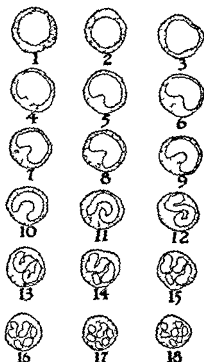
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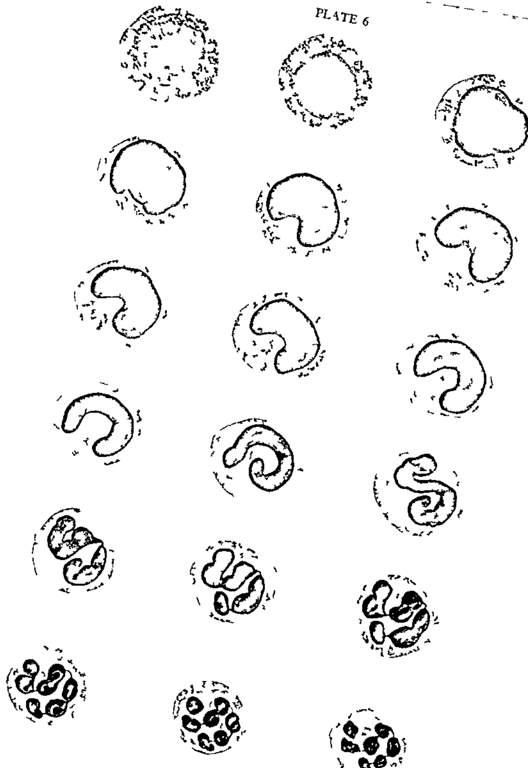
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PLATE 6

THE DEVELOPMENT OF A MYELOCYTE



1 Young myelocyte with blue cytoplasm and brilliant granulation
2 and 3 Later myelocytes
4 and 5 Young juveniles with slight indentation of nuclei and a retention of blue in the cytoplasm
6 7 8 and 9 Juveniles maturing by indentation of nuclei and development of a more delicate type of granulation
10 Band (staff or stab form of Schilling)
11 Band showing narrowing and curling of nucleus
12 Band just preceding segmentation
13 Segmenter with two lobes separated by a filament of chromatin
14 Segmenter with three lobes separated by two filaments
15 Segmenter with four lobes separated by three filaments
16 Segmenter with five lobes separated by four filaments (hypersegmented)
17 Segmenter with six lobes separated by five filaments (the senile neutrophil)
18 Segmenter with seven lobes separated by six filaments



5

Lymphocytes and Monocytes

(See Plates 7 and 8, pp 40-43)

LYMPHOCYTES

Because of morphologic variation in the lymphocytic cells Plate 7 is designed to show the various types that may be seen not only under normal conditions but in various diseases Cells 1 to 6 could be classified as lymphoblasts since the nuclei of these show either clear nucleoli or suggestions of nucleoli varying from *one to three in number* *Cell 4* shows a large vacuole in the cytoplasm Cells *7 to 12 are classified as* large lymphocytes in which the amount of cytoplasm is relatively abundant usually sky blue in color nuclear chromatin arranged in coarse loose and deep staining masses and a suggestion of a rather clear perinuclear halo The young type of lymphocyte as shown in these larger forms is thought to be a precursor of the smaller types as seen in cells 13 to 18 Atypical forms of both large and small lymphocytes are seen in various diseases accom*panied by* lymphocytic stimulation Infectious mononucleosis is the best *example of this*

Under normal conditions lymphocytes have *their origin from the retic*ular cells of lymph follicles but under abnormal conditions such as leukemia they probably arise also from the primitive free cells in the bone marrow The function of lymphocytes seems to be chiefly a mechanical one They are especially active in walling off chronic inflammatory foci *and are found to be increased in* chronic inflammatory states Al*though they constitute from 20 to 30* per cent of the circulating leukocytes and are somewhat motile they play little part in phagocytosis It has been suggested that they are active in antibody production

Both large and small lymphocytes are found normally in the blood stream In children there is a predominance of large lymphocytes and even lymphoblasts may be found in *considerable numbers in conditions* characterized by marked lymphocytic *cellular response In the usual differ*ential count there is no need to separate large from small lymphocytes since increases of both have the same significance

MONOCYTES

Plate 8 shows the various types of *monocytes that may be seen in pe*ripheral blood and illustrates the var*ious cytologic patterns and extreme* morphologic variability of monocytes *which frequently lead to confusion* with other cell types Cells 1 to 3 can

be classified as monoblasts They show either one or two distinct nucleoli in the nucleus The other monocytes on this plate can be considered to be either young or adult forms that may be found in peripheral blood These cells are characterized by marked variation in shape because of their irregular cytoplasmic protrusions There is also variation in the nuclear structures since the nuclei are irregular in shape and frequently show overfolding marked indentation and pseudopodial projections There is also irregularity in cytoplasmic granulation since some monocytes are apparently free of granules while others show a heavy fine azure like granulation throughout the cytoplasm and still others show small groups of similar granulation in isolated cytoplasmic areas

Monocytes have been called by a variety of names including endotheliocytes endothelial cells transitional cells large mononuclears etc Some writers believe that monocytes are derived from myeloblasts others that they are derived from lymphoid elements and still others that these cells arise from their own specific cell type This accounts to some extent for the fact that monocytic leukemia has been divided into two cellular categories—one that appears to be a monocytoid phase of myelogenous leukemia and the other a reticuloendotheliosis

Monocytes are the chief phagocytic cells of the blood They are capable of ingestion of foreign debris and particulate matter by the process of extrusion of cytoplasmic pseudopodia and ingestion of the material They serve an important function in walling off inflammatory foci of infection Monocytes are peroxidase positive and are frequently confused with the juvenile types of neutrophils

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Both large and small lymphocytes are found normally in the blood stream In children there is a predominance of large lymphocytes and even lymphoblasts may be found in considerable numbers in conditions characterized by marked lymphocytic cellular response In the usual differential count there is no need to separate large from small lymphocytes since increases of both have the same significance

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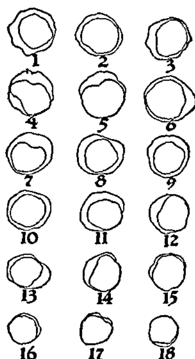
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PLATE 7

LYMPHOCYTES



1 2 3 and 6 Lymphoblasts drawn from a case of acute lymphatic leukemia
4 Large lymphocyte with lobulated nucleus and vacuole in the cytoplasm drawn from a case of infectious mononucleosis (Lymphoblast?)
5 and 7 Large lymphocytes with azure granulation
8 9 10 11 and 12 Large lymphocytes
13 14 15, 16 17 and 18 Intermediate and small lymphocytes

PLATE 7













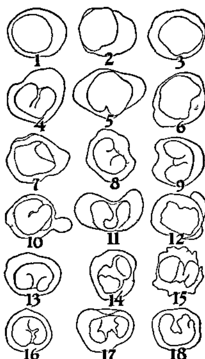







PLATE 8

MONOCYTES



1 Monoblast with one nucleolus and light blue cytoplasm
2 Monoblast with two nucleoli
3 Monoblast with dark basophilic cytoplasm and one vacuole
4 Young monocyte with indented nucleus and no cytoplasmic granules
5 Young monocyte with four vacuoles in the cytoplasm
6 7 and 8 Monocytes with slightly indented nuclei and azure granulation
9 Monocyte with mature nucleus and no cytoplasmic granules
10 Monocyte with a long overfolding nucleus a cytoplasmic pseudopod and a granular cytoplasm
11 Monocyte with excessive granulation
12 Monocyte with two pseudopodia and no granules
13 and 16 Monocytes with blue nongranulated cytoplasm
14 and 17 Monocytes with azure granulation near the Hof of the nucleus
15 Monocyte with irregular cytoplasmic border
18 Mature monocyte with horseshoe nucleus and small azure granules scattered over the surface of the cytoplasm





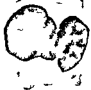















6

The Red Cells

(See Plates 9 and 10 pp 46-49)

ERYTHROBLASTS (NUCLEATED ERYTHROCYTES)

Plate 9 shows various types of nucleated red cells that may be found in *the bone marrow and rarely in the* peripheral blood Cells 1 through 4 show various types of megaloblasts in stages of division Such cells are seen only in the bone marrow except in rare conditions such as leukemia where an occasional one may be found in peripheral blood Cells 5 and 6 are megaloblasts and cells 7 through 11 are macroblasts the remainder being normoblasts of various types including small forms which are known as microblasts

The erythrocytes have their origin from the endothelium lining the capillary sinusoids of the bone marrow Conditions most favorable for normal erythropoiesis include a collapsed capillary bed a sluggish blood flow and low oxygen tension Under normal conditions this state of affairs prevails within the bone marrow to a sufficient extent to maintain the circulating erythrocytes at a normal level The beginning of red-cell maturation is apparently swelling of the blood vessel endothelium followed by division The result is that the outer cell becomes the endothelial wall and the inner cell a megaloblast the earliest stem cell of the erythrocyte The maturation order therefore extends from the endothelial cell to the megaloblast then to the early macroblast the late macroblast the normoblast the reticulocyte and finally the erythrocyte

When the megaloblastic stage has been reached its development seems to be governed by the presence of an adequate amount of so-called antianemic factor or X hematopoietic factor which is lacking in pernicious anemia and is found in liver extract Lack of this factor in the bone marrow will result in a macrocytic anemia and a marrow that is crowded with relatively large number of megaloblasts At any point during this cycle from the megaloblastic to the normoblastic stage the nucleated red cell is capable of repeated divisions and there is evidence that normoblasts reproduce themselves at a more rapid rate than the more immature forms Beginning at the normoblastic stage the cell begins to develop hemoglobin within its cytoplasm and at this point iron is the most important factor responsible for the continued maturation of the cell

Megaloblasts are present in small

numbers in normal bone marrow but they never appear in normal blood They are found in the peripheral blood only in conditions where the hematopoietic principle is lacking or the normal maturation of the cell is arrested in the marrow Thus they may be seen in peripheral blood in pernicious anemia in relapse and other macrocytic anemias of a similar type

Macroblasts and normoblasts constitute from 80 to 90 per cent of the bone marrow erythroid elements These cells may appear in peripheral blood when the erythroid elements have been subjected to intensive stimulation usually by reason of blood loss or blood destruction Under ordinary conditions the bone marrow responds to this stimulation by producing increased numbers of reticulocytes but under unusual conditions it produces normoblasts in such number that they appear in the peripheral blood

Normoblasts are frequently found in the so-called bone marrow crisis when the marrow has become physiologically exhausted and red-cell production is unable to keep pace with red-cell destruction or in cases of extreme hyperplasia of the marrow

Microblasts occur only in those situations in which there is functional exhaustion of the marrow combined with iron deficiency so that the resulting nucleated red cell is microcytic in character The presence of nucleated red cells in the blood is nearly always accompanied by reticulocytosis except when the nucleated cells are chiefly megaloblasts

ERYTHROCYTES

Plate 10 shows the various types of erythrocytes that might be encountered in a study of bone marrow or peripheral blood Erythrocytes can be classified according to size the larger ones being known as macrocytes the normal ones as normocytes and the smaller ones as microcytes They are also classified according to hemoglobin content those containing more than the normal amount of hemoglobin being referred to as hyperchromic those with a normal amount being normochromic and those with less than normal being called hypochromic Some erythrocytes may show distortion from their normal pink color and such a condition is referred to is polychromatophilia

Cells 1 to 4 are macrocytes showing variations in color based upon hemoglobin content Cells 13 to 16 are reticulocytes or young red cells Cells 17 to 24 show various types of basophilic degeneration Cells 25 to 28 show irregular shapes this condition being spoken of as poikilocytosis Cells 29 to 32 are sickle cells as seen in sickle cell anemia These are sometimes called meniscocytes and the condition meniscocytosis Cells 33 to 36 are oval cells seen in the condition referred to as ovalocytosis If red cells are found to vary considerably in size some being small and others large the condition is referred to as anisocytosis

The normal circulating erythrocyte of the human being is about seven and one half micra in diameter and is a biconcave disk from two to three micra in thickness Thus it is

6

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ERYTHROCYTES

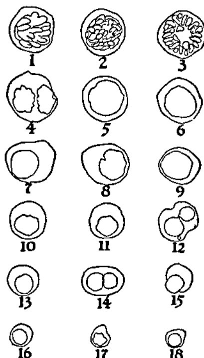
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PLATE 9

NUCLEATED ERYTHROCYTES (ERYTHROBLASTS)



1 2 3 and 4 Megaloblast in division
5 and 6 Early megaloblasts
7 8 and 9 Early macroblasts
10 and 11 Late macroblasts
12 Erythroblast in process of karyorrhexis with basophilic stippling in cytoplasm
13 Normoblast
14 Normoblast in division
15 Normoblast with nuclear extension or eccentric nucleus
16 17 and 18 Microblasts

PLATE 9













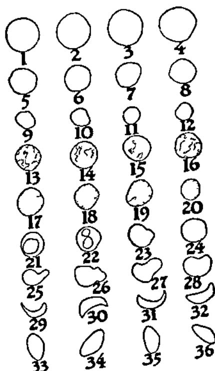







PLATE 10

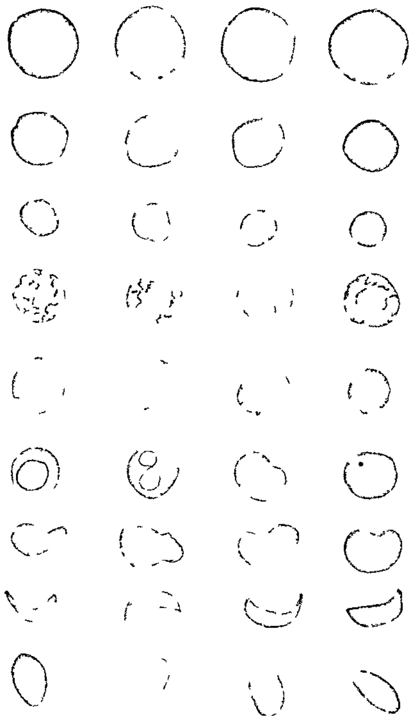
ERYTHROCYTES



1 Hyperchromic macrocyte
2 Normochromic macrocyte
3 Hypochromic macrocyte
4 Polychromatophilic macrocyte
5 Hyperchromic normocyte
6 Normochromic normocyte
7 Hypochromic normocyte
8 Polychromatophilic normocyte
9 Hyperchromic microcyte
10 Normochromic microcyte
11 Hypochromic microcyte
12 Polychromatophilic microcyte

13 14 15 and 16 Reticulocytes
17 18 19 and 20 Erythrocytes with basophilic stippling
21 and 22 Cabot ring bodies
23 and 24 Howell Jolly bodies
25 26 and 27 Poikilocytes
28 Polychromatophilic poikilocyte
29 30 and 31 Sickle cells (meniscocytes)
32 Polychromatophilic sickle cell
33 34 and 35 Ovalocytes
36 Polychromatophilic ovalocyte

PLATE 10



so designed as to have a maximum surface area to facilitate the exchange of gases Since the central portion of the cell is thinner than the edge this accounts for the central pallor seen in normal red cells and called achromia

The red cell consists of an organic stroma with hemoglobin the most important constituent, comprising about 30 per cent of its bulk which is about 30 micromicrograms per cell It has an outer semipermeable cell membrane It contains quantities of phosphatides cholesterol glucose urea creatinine glutathione nucleotides and various inorganic chemicals including small quantities of copper and iron The total solid constituents are proteins 4 per cent hematin 4 3 per cent and globin 89 5 per cent The cell acts as a passive vehicle for the transportation of hemoglobin, which carries oxygen to the tissues and removes carbon dioxide

The life span of the red cell is about 30 days Red cells are produced and flushed into the blood stream at the rate of about two or three trillion each day or nearly two billion per minute An equal number of cells are destroyed under normal conditions probably by the process of hemolysis and eventual phagocytosis by the reticulo-endothelium Many undergo fragmentation in the blood stream and fragments are removed by reticulo-endothelial phagocytes Hemoglobin is set free and broken down into globin and hematin The hematin loses its iron content and is finally changed into bilirubin and eventually into bile pigment The spleen plays the important role in this destructive process

The number of red cells increases with exercise since many of them are stored in the splenic reservoir normally They increase quickly during passage from low to high altitudes and the count may increase as much as one million per cubic millimeter in 24 hours under such conditions When red cells are suspended in their own plasma or serum they stack up on each other This is known as rouleaux formation This is most marked in saline concentrations of about 7/10 of 1 per cent When red cells are placed in hypotonic salt concentrations they undergo swelling and hemolysis and eventual destruction If placed in hypertonic solutions of salt they become shrunken and crenated

The reticulocyte is the intermediate stage between the nucleated red cell and the adult nonnucleated cell From about ½ to 1 per cent of the normal red cells are reticulocytes The reticulocyte is slightly larger than the mature red cell and its duration of life is thought to be about five days When the reticulum disappears the next step in red cell development is the appearance of a single highly refractive granule which apparently precedes the fully matured cell

Reticulocytosis is always a sign of red-cell regeneration and increased marrow activity It always precedes a general rise in the total erythrocyte count For this reason reticulocytosis is considered the most accurate index as to the efficacy of liver therapy Reticulocytes are normally increased in the newborn in pregnancy and in all anemias characterized by excessive bone marrow activity They are markedly decreased in conditions of

bone marrow aplasia and also in pernicious anemia and other macrocytic anemias in relapse

Reticulocytes should always be estimated and stated in total numbers rather than in percentage of cells present If the normal red-cell count is five million per cubic millimeter and 1 per cent of these are reticulocytes then under normal conditions there should be about fifty thousand reticulocytes per cubic millimeter In a case of severe anemia if the total red-cell count is one million per cubic millimeter and 5 per cent of these are reticulocytes this will result also in a total of fifty thousand per cubic millimeter Reticulocyte counts as high as 95 per cent of the total number of red cells have been recorded

7

Normal Blood

(See Plate 11 pp 54, 55)

The hematologic system consists of all circulating blood and all blood forming tissues This collective group *of organs and tissues is known as the* hemiton It is divided functionally into three organs or units known as the erythron the leukon and the thrombon The erythron includes the circulating erythrocytes and the fixed erythropoietic tissue of the bone marrow sinusoids The leukon consists of the myeloid elements of the bone marrow and the granular leukocytes the lymphoid elements and the lymphocytes and the reticulo-endothelium and the monocytes The thrombon includes all thrombocytes and their precursors the megakaryocytes of the bone marrow

The total cellular elements of the blood comprise about 45 per cent of the total blood volume in the male and about 42 per cent in the female and conversely the blood plasma the liquid in which the cells are suspended comprises about 55 and 58 per cent of the total blood volume respectively *This can be determined in* any case by adding a quantity of blood to a suitable anticoagulant centrifuging the specimen at high speed and noting the degree of cell packing that results This is known as the hematocrit reading The total blood volume of the body depends upon body weight and surface areas and varies somewhat with the method employed for its measurement The volume is considered to be about one twelfth of the body weight so that the adult of average size has about six thousand cubic centimeters of blood

NORMAL HEMATOLOGIC STANDARDS

Adults

Hemoglobin
- Men 14 5 to 16 9 Gm per 100 cc of blood
- Women 12 5 to 15 0 Gm per 100 cc of blood

Erythrocytes
- Men 4 5 to 5 5 million per cu mm of blood
- Women 4 0 to 5 0 million per cu mm of blood

Leukocytes
- Men and women 5 000 to 10 000 per cu mm of blood

Differential Count

	Relative values (per cent)	*Absolute values (per cu mm of blood)*
Neutrophils	60 70	3000 6000
Basophils	0 5 1	0 100
Eosinophils	1 3	50 300
Lymphocytes	20-40	2000 4000
Monocytes	2 6	200 600

Color Index 1 0
Volume of Packed Cells
Men 45 cc per 100 cc of blood
Women 42 cc per 100 cc of blood
Volume Index 1 0
Mean Corpuscular Hemoglobin
27 to 32 micromicrograms
Mean Corpuscular Hemoglobin Concentration
33 to 38 per cent
Mean Corpuscular Volume
80 to 94 cubic micra
Reticulocytes 0 5 to 1 0 per cent of erythrocytes (25 000 to 50 000 per cu mm)
Platelets 250 000 to 350 000 per cu mm of blood (Fonio s method)
500 000 per cu mm of blood (Olef's method)
Coagulation Time
2 to 6 minutes (slide method)
3 to 8 minutes (capillary tube method)
5 to 8 minutes (Lee and White s method)
Bleeding Time 2 to 3 minutes
Clot Retraction Time Beginning retraction in from 1 to 6 hours
Resistance of Erythrocytes to Hypotonic Salt Solution
Beginning hemolysis from 0 44 to 0 42 per cent NaCl
Complete hemolysis from 0.34 to 0.32 per cent NaCl
Icterus Index 1 to 5 units
Van den Bergh Reaction Indirect normal serum contains from 0 1 to 0 3 mg bilirubin per 100 cc of blood

New born Infants

Hemoglobin 100 to 140 per cent
Erythrocytes 5 to 7 5 million per cu mm of blood
Leukocytes 15 000 to 25 000 per cu mm of blood
Platelets 200 000 to 400 000 per cu mm of blood

Within the first three months of life there is a physiologic decrease in red cells and hemoglobin This is caused apparently by decrease in marrow activity because of high oxygen tension of extra uterine life and a destruction of red cells by hemolysis They level out to about the normal figure at the end of the sixth month Immediately after birth there is neutrophilic leukocytosis which declines to about 30 per cent neutrophils at the end of the first three or four weeks During childhood there is a relative lymphocytosis with the lymphocyte percentage being around 50

Hemoglobin and red cells are slightly higher in normal people living in high altitudes In the United States at 1000 feet above sea level the average hemoglobin is 15 03 gm per 100 cc of blood and the average red cells 5 1 million per cu mm of blood There are no significant differences between city and country residents nor between men working out of doors and within doors and none between healthy male Negroes and whites Red cell values are the same in all races

CHEMICAL CONSTITUENTS OF BLOOD

Nonprotein Nitrogen 25 to 30 mg per 100 cc of blood
Urea 12 to 15 mg per cent
Uric acid 1 to 3 mg per cent
Creatinine 1 to 2 mg per cent

Sugar 80 to 120 mg per 100 cc of blood

Chlorides
In plasma 570 to 600 mg per cent
In cells 285 to 300 mg per cent

7

Normal Blood

(See Plate II, pp. 54-55)

The hematologic system consists of all circulating blood and all blood forming tissues. This collective group of organs and tissues is known as the hematon. It is divided functionally into three organs or units known as the erythron, the leukon and the thrombon. The erythron includes the circulating erythrocytes and the fixed erythropoietic tissue of the bone marrow sinusoids. The leukon consists of the myeloid elements of the bone marrow and the granular leukocytes, the lymphoid elements and the lymphocytes, and the reticulo-endothelium and the monocytes. The thrombon includes all thrombocytes and their precursors, the megakaryocytes of the bone marrow.

The total cellular elements of the blood comprise about 45 per cent of the total blood volume in the male and about 42 per cent in the female, and conversely the blood plasma, the liquid in which the cells are suspended, comprises about 55 and 58 per cent of the total blood volume, respectively. This can be determined in any case by adding a quantity of blood to a suitable anticoagulant, centrifuging the specimen at high speed and noting the degree of cell packing that results. This is known as the hematocrit reading. The total blood volume of the body depends upon body weight and surface areas and varies somewhat with the method employed for its measurement. The volume is considered to be about one twelfth of the body weight, so that the adult of average size has about six thousand cubic centimeters of blood.

NORMAL HEMATOLOGIC STANDARDS

Adults

Hemoglobin
- Men: 14.5 to 16.9 Gm. per 100 cc. of blood
- Women: *12.5 to 15.0 Gm. per 100 cc. of blood*

Erythrocytes
- Men: 4.5 *to 5.5 million per cu. mm.* of blood
- Women: 4.0 to 5.0 million per cu. mm. of blood

Leukocytes
- Men and women: 5,000 to 10,000 per cu. mm. of blood

Differential Count

	Relative values (per cent)	*Absolute values (per cu. mm. of blood)*
Neutrophils	60-70	3000-6000
Basophils	0.5-1	0-100
Eosinophils	1-3	50-300
Lymphocytes	20-40	2000-4000
Monocytes	2-6	200-600

PLATE 11

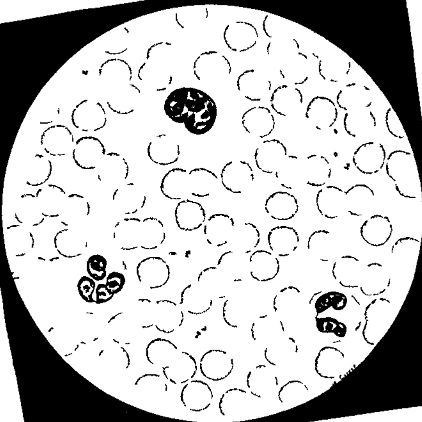
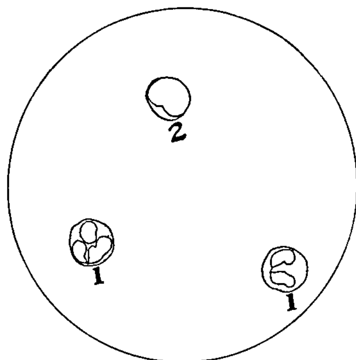


PLATE 11

NORMAL BLOOD



1 Neutrophils
2 Lymphocyte

Blood findings (normal adult)	
Hemoglobin	16 Gm (Newcomer's method)
R B C	5 100 000 per cu mm
W B C	200 per cu mm
Platelets	350 000 per cu mm

Erythrocytes normochromic and normocytic

Differential	
Myelocytes	0%
Juveniles	0%
Bands	1%
Segmenters	63%
Total neutrophils	64%
Lymphocytes	33%
Monocytes	2%
Eosinophils	1%

8

Leukocytosis

(NEUTROCYTOSIS LYMPHOCYTOSIS MONOCYTOSIS EOSINOPHILIA)

(See Plates 12 13 14 15 pp 58 59 62-65 68 69)

NEUTROPHILIC LEUKOCYTOSIS

Leukocytosis is that condition in which the total number of circulating leukocytes exceeds the normal This may be caused by an increase in any one of the various leukocytes The most common type is neutrophilic leukocytosis or neutrocytosis or if caused by the lymphocytes it is a *lymphocytic leukocytosis* or lymphocytosis or if caused by an increase in eosinophils it is an eosinophilic leukocytosis or eosinophilia

Many factors govern the number of leukocytes in the normal person The range of normal varies between 5 000 and 10 000 cells per cu mm The cell count varies in the same person on different days and in the same person at different times of the same day The average is about 8 000 per cu mm in healthy medical students and from about 10 000 to 12, 000 in infants because of the larger number of lymphocytes It is important to estimate numbers of white cells not only in percentage but in total numbers per cubic millimeter of blood

PHYSIOLOGIC LEUKOCYTOSIS

There is a diurnal tide of leukocytosis because there are two periods during the day when the leukocytes are increased sightly in number—from 10 00 to 11 00 A M and from 11·00 to 12·00 P M Also the leukocytes are delivered from the bone marrow into the peripheral circulation *about twice each hour* The number of leukocytes is influenced by food intake Usually after intake of a heavy meal during the period of digestion there is a so-called digestive leukocytosis However it is thought that a leukopenia exists in some people at that time particularly if they have ingested food to which they may be sensitive and in order to determine this the original measurements of leukocytes should be at the basal or *resting state*

There is a physiologic leukocytosis of pregnancy The full *term* pregnant woman has a leukocyte count of from 10 000 to 20 000 cells per cu mm., particularly in the third trimester There is also neutrophilic leukocytosis of the newborn infant,

Calcium 9 to 11 mg per cent in the plasma of adults slightly higher in that of children

Serum Protein total 6 to 8 Gm per 100 cc of blood

Albumin 4 5 to 5 5 Gm per cent

Globulin 1 5 to 3 0 Gm per cent

CO_2 Combining Power of the Plasma 55 to 80 cc of carbon dioxide per 100 cc of plasma

Cholesterol 150 to 200 mg per 100 cc of blood

EXAMINATION OF BLOOD

The preliminary examination of the blood of a patient with a suspected blood disease should include the following procedures

Estimation of hemoglobin
Erythrocyte count
Leukocyte count
Differential count
Color index
Volume index
Reticulocyte count
Fragility test (in cases of splenomegaly)
Coagulation time
Clot retraction time
Platelet count
Wassermann or Kahn reaction
Icterus index

For the technic of carrying out the above procedures see chapter on technics

PLATE 12

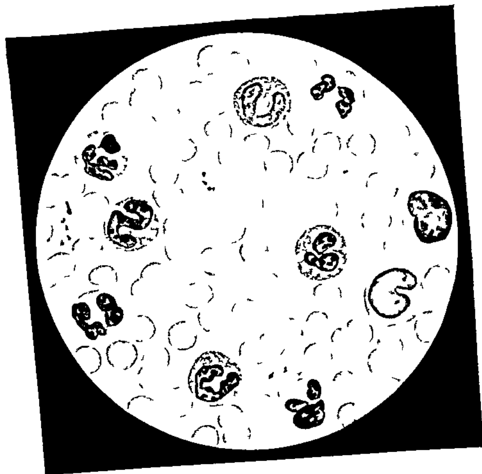
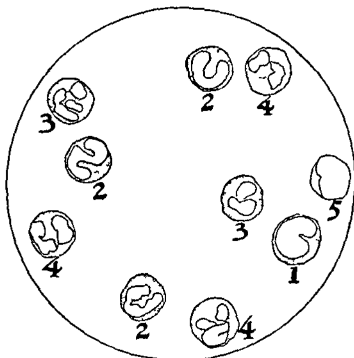


PLATE 12

NEUTROPHILIC LEUKOCYTOSIS



1 Juvenile neutrophil
2 Band neutrophils (toxic granulation)
3 Segmented neutrophils (toxic granulation)
4 Segmented neutrophils (normal granulation)
5 Lymphocyte

Blood findings (patient with lobar pneumonia)

Hemoglobin	15 Gm (Newcomer's method)
RBC	4 850 000 per cu mm
WBC	40 200 per cu mm
Platelets	240 000 per cu mm

Erythrocytes normochromic and normocytic

Differential		
Myelocytes	1%	
Juveniles	10%	
Bands	31%	
Segmenters	46%	
Total neutrophils		88%
Lymphocytes		9%
Monocytes		3%

ence of band forms of neutrophils and one juvenile Of even greater importance than the total leukocyte count is the shift to the left as indicated by the Schilling classification (see page 34) The marked left shift toward granular-cell immaturity indicates a rather intensive and severe bone marrow stimulus A marked left shift with a total low leukocyte count would appear to have more serious prognostic import than a similar left shift with a high leukocyte count A low total count probably means that the available circulating cells have been drawn to the site of infection In the usual infection this is only temporary and the count will rise as soon as the marrow output becomes adequate

LYMPHOCYTOSIS (See Plate 13)

The normal number of circulating lymphocytes is between 2000 and 4000 cells per cu mm in adults and between 4000 and 6000 per cu mm in children Since lymphocytes are cells whose major function is mechanical in walling off inflammatory processes they are usually increased in all conditions characterized by chronic inflammation and in conditions characterized by lymphoid hyperplasia Thus there is lymphocytosis in such diseases as glandular tuberculosis pulmonary tuberculosis in the more chronic phases secondary syphilis Hodgkin s disease lymphosarcoma and infectious mononucleosis General lymphadenopathy from whatever cause may give rise to increased numbers of lymphocytes. It is seen in many disease entities such as typhoid fever typhus fever undulant fever chronic malaria smallpox chickenpox and measles In whooping cough the lymphocytic response is especially severe

Lymphocytosis is not seen as a result of invasion with pyogenic organisms since this is nearly always followed by a neutrophilic response Lymphocytosis may follow various vaccination procedures It is seen in the so-called roseola infantum or exanthem subitum of children A lymphatic reaction is frequently encountered in exophthalmic goiter and hyperthyroidism and lymphocytosis may precede the involutional changes in the gland The lympocytic response in infectious mononucleosis is especially marked with various atypical forms seen in the peripheral blood Any disease even though it be a pyogenic one in the beginning that requires a long period for healing and is characterized by chronicity may present a lymphocytosis often called postinfectious lymphocytosis

In tuberculosis a predominance of lymphocytes usually indicates a healing process whereas diminished lymphocytes and increased monocytes indicate a period of relative activity This has resulted in the development of the so-called monocytic lymphocytic ratio which is used as a criterion to evaluate the progress of a tuberculous patient The lymphocytes seen in these conditions are usually of the small adult type and younger forms are rarely encountered In lymphatic leukemia the total number of circulating lymphocytes reaches extremely high levels and the cells may show varying grades of immaturity depending on the type of leukemia

which may be as high as 20 000 cells per cu mm The leukocytes are increased because of muscular activity This may be caused by increased adrenalin output or by muscular contractions by which leukocytes are mechanically forced into the peripheral circulation Leukocytes are increased during periods of fright, anger emotional upsets etc This is probably caused by stimulation of the sympathetic nervous system with release of adrenalin When this occurs there is very little change in the differential cell count It is probably caused by overactivity of the adrenal glands followed by dilatation of the vascular bed constriction of the spleen and the forcing of the leukocytes into the peripheral circulation Artificial fever will cause increased numbers of white cells but only for a short time and it is possible that increased temperature as such may be responsible for leukocytosis

PATHOLOGIC LEUKOCYTOSIS

Since the neutrophil is the most actively ameboid cell of the body and its chief function is to ward off bacterial invasion these cells therefore constitute the first line of defense in many infectious diseases They not only help wall off infection and release proteolytic ferments which break down bacteria and cellular material into necrotic debris but ingest and devour bacteria by phagocytic action The leukocytes that are killed in such conditions form a mass of dead cellular debris known as pus In these situations the neutrophils are usually increased in the blood and there is nearly always a shift to the left toward granulocytic immaturity indicating that considerable bone marrow stimulation accompanies the process Any disease that is caused by infection with a so-called pus producing or pyogenic organism will call forth a neutrophilic leukocytosis Thus variable degrees of leukocytosis are seen in such infections as single or multiple abscesses whatever their location particularly those caused by staphylococci and streptococci pneumonia peritonitis otitis media mastoiditis meningitis furuncles solitary abscesses scarlet fever, diphtheria erysipelas etc Furthermore the injection of irritating chemicals will produce leukocytosis as for example the formation of a sterile abscess in the muscle by the injection of turpentine

There is evidence that dead and necrotic tissue itself will produce leukocytosis as seen for example after myocardial infarction from coronary thrombosis where no infectious element is involved Leukocytosis may follow acute hemorrhages particularly if the blood loss is considerable It is the rule in various malignancies particularly in those that are far advanced regardless of their location There is a postoperative leukocytosis that is probably caused by tissue damage and trauma during the operative procedure Neutrophilic output will follow the injection of many inert materials such as carbon dead bacteria preparations of various metals sterile milk etc

Plate 12 shows a typical neutrophilic leukocytosis in which there is considerable evidence of cellular immaturity as indicated by the pres

PLATE 13

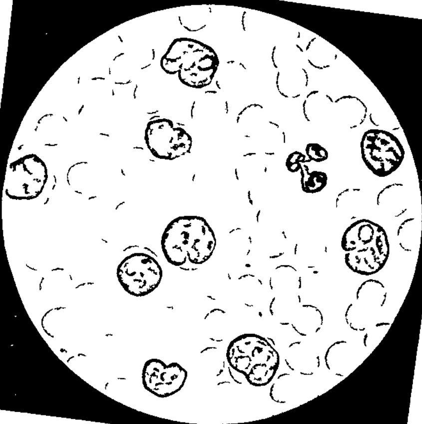
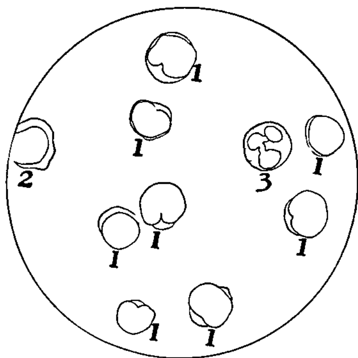


PLATE 13

LYMPHOCYTOSIS



1 Lymphocytes
2 Lymphocyte with azure granules
3 Neutrophil

Blood findings (child with whooping cough)

Hemoglobin	16.[illegible] Gm. (Newcomer's method)	Differential	
R.B.C.	5,350,000 per cu. mm.	Myelocytes	0%
W.B.C.	39,000 per cu. mm.	Juveniles	4%
Platelets	310,000 per cu. mm.	Bands	6%
		Segmenters	10%
		Total neutrophils	20
		Lymphocytes	80%

Erythrocytes: normochromic and normocytic

PLATE 14

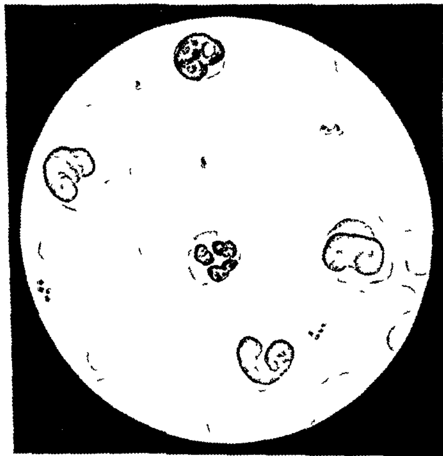
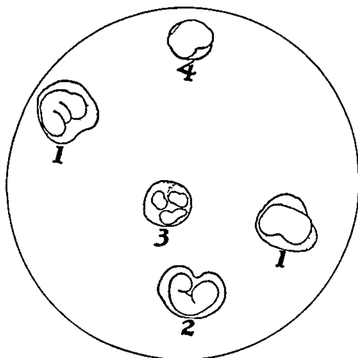


PLATE 14

MONOCYTOSIS



1 Monocytes with granular cytoplasm
2 Monocyte without granulation
3 Neutrophil
4 Lymphocyte

Blood findings (patient with active pulmonary tuberculosis)

Hemoglobin	14 5 Gm (Newcomer s method)
R B C	4 500 000 per cu mm
W B C	10 200 per cu mm
Platelets	292 000 per cu mm

Erythrocytes normochromic and normocytic

Differential	
Myelocytes	0%
Juveniles	2%
Bands	8%
Segmenters	56%
Total neutrophils	66%
Lymphocytes	16%
Monocytes	18%

such conditions the nasal and the oral secretion of allergic patients will show more eosinophils than normal The fluid of blebs and wheals in the allergic phenomena becomes filled with eosinophils Eosinophilia may be a consistent finding in a number of skin diseases including psoriasis pemphigus various types of pruritis and different forms of eczema There is usually a marked eosinophilia after the bite of the black widow spider Eosinophils may be increased during the healing phase after acute infections Appendicitis is sometimes designated as subacute because of eosinophilic infiltrations into the submucosal appendiceal layer Also there may be eosinophilia in other infectious diseases in the chronic stages It has been observed frequently in certain types of arthritis It is seen in some cases of periarteritis nodosa and also has been reported in cases of chronic benzene poisoning Increased eosinophils may occur in the blood in the later stages of pneumonia and this has been stated to be of good prognostic import Many observers have noted the eosinophilia that follows the treatment of patients with various preparations of liver extract particularly if the liver extract is given by oral administration

INCREASED BASOPHILS

Apparently there is no such condition as a basophilic leukocytosis and there is no infectious disease that is characterized by basophilia or increased basophils These cells are seen in substantial numbers only in cases of chronic myelogenous leukemia in which they may be increased in certain cases Furthermore the function of the basophil is unknown although at least 25 different hypotheses have been suggested

PLASMA CELLS

Under normal conditions plasma cells are not found in the blood These cells are probably atypical forms of lymphocytes and have their origin from lymphoid tissue Although seen quite commonly in fixed tissue in response to subacute infectious diseases they are remarkable because of their rare appearance in the blood No doubt their function is similar to that of lymphocytes They have been reported to be increased in German measles in some cases of multiple myeloma and in rare cases of plasma cell leukemia they may be present in large numbers Furthermore they have been reported in rare instances of syphilis Even though they are notably increased in the tissues in such diseases as lupus various granulomata of the skin in tubercles plasma cell myelomata etc., these changes are rarely reflected in the blood

MONOCYTOSIS (See Plate 14)

Monocytes comprise from 5 to 10 per cent of the circulating white cells or from about 500 to 1000 cells per cu mm The function of monocytes is primarily phagocytic and they are increased in various conditions in which phagocytosis is required Monocytosis may be seen in pigeons after the injection of tubercle bacilli and in certain anginal conditions of the soft tissues of the mouth Monocytes are usually increased in the more active phases of malaria

There is usually a monocytosis in practically any type of infectious disease that might be designated clinically as subacute Thus monocytes are seen in various stages of lymphogranulomata, syphilis tuberculosis during the active and progressive phase typhoid fever in the early stages Hodgkin s disease in the chronic stages of amebic dysentery and possibly in infectious mononucleosis Also there is usually monocytosis after removal of the spleen The number of monocytes may reach extremely high levels in cases of monocytic leukemia

It should be emphasized that monocytosis is not characteristic of any certain disease that it occurs in many diseases at various times and that it is a phagocytic response for the ingestion and the removal of large living and dead organisms and foreign material Furthermore certain diseases in the acute phases may be characterized by neutrophilic leukocytosis in the later stages by monocytosis and in the more chronic forms by lymphocytosis The type of cellular response that is seen in the blood is dependent upon the type of infection and the type of tissue response provoked by the infectious agent

EOSINOPHILIA (See Plate 15)

The total number of circulating eosinophils varies from 1 to 2 per cent of all white cells or from 100 to 200 cells per cu mm The eosinophil contains a type of cytoplasmic granulation in which the granules are large very shiny and refractile more acidophilic in character and stain a bright orange red The granulation is peroxidase positive The granules do not show the characteristics of fat

There is evidence to indicate that eosinophils may on rare occasions be increased in individuals who are normal Furthermore there are many records of classic familial hereditary eosinophilia in which the total number of eosinophils reaches extremely high levels in individuals presumably otherwise normal Certain diseases are known to be accompanied by eosinophilia these including intestinal infestation with various parasites such as hookworms tapeworms including the fish tapeworm the roundworms the pinworms and others Eosinophilia is seen to an extreme degree in trichiniasis and is found in certain stages of amebiasis and filariasis It may be found in the healing phase of scarlet fever

Practically all types of the so-called allergic diseases are accompanied by eosinophilia so that it is seen in such conditions as asthma hay fever angioneurotic edema and other allergic or hypersensitive states In

PLATE 15

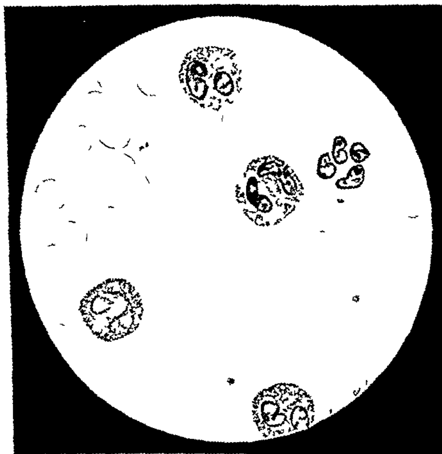
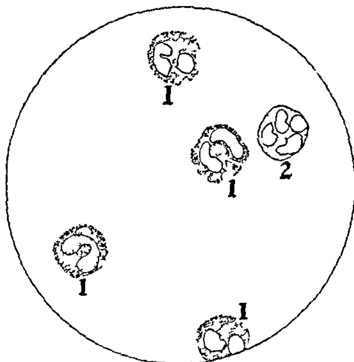


PLATE 15

EOSINOPHILIA



1 Eosinophils (showing color variation in cytoplasmic granulation)
2 Neutrophil

Blood findings (patient with trichiniasis)		Differential	
Hemoglobin	12 6 Gm (Newcomer s method)	Myelocytes	0%
R B C	4 340 000 per cu mm	Juveniles	3%
W B C	11 800 per cu mm	Bands	5%
Platelets	320 000 per cu mm	Segmenters	34%
		Total neutrophils	42%
Erythrocytes slightly hypochromic and normocytic		Lymphocytes	20%
		Eosinophils	38%

destroyed in excessive numbers by the spleen and the resulting syndrome is called primary splenic neutropenia

Severe leukopenia can be produced in experimental animals by the intra muscular injection of small daily doses of benzene and when given in very small doses the chemical seems to exert a selective affinity for leuko poietic elements so that study of the marrow shows leukopoietic aplasia with other elements relatively unaf fected Since benzene is the central nucleus for so many drugs and chem icals in current medical use any preparation which contains it must be under suspicion with regard to its ability to produce leukopenia in oc casional individuals Thus it is now definitely established that amidopy rine and all its various combinations arsphenamine dinitrophenol the var ious sulfonamide drugs the benzene ring containing gold salts and certain organic arsenical preparations are all capable of producing severe grades of leukopenia In every case of leu kopenia a careful history should be taken to exclude or establish the in gestion or exposure to these various drugs

Physical agents such as radiation can also damage the marrow to the point of leukopenia as seen in such conditions as radiation osteitis from radium and excessive exposure to roentgen rays can also produce severe leukopenia Granulocytic leukopenia has been observed in monkeys after prolonged feeding with diets defi cient in vitamin C Similar leuko penic states with ulcerative stomatitis have been produced in dogs fed on a deficiency diet that produces black tongue Some instances of leuko- penia therefore may be dietary in origin The feeding of succinylsulfa thiazole to laboratory animals will consistently produce leukopenia in spite of the fact that this particular sulfonamide preparation is not ab sorbed from the intestinal tract to any considerable extent If it can be ascertained that leukopenia is the re sult of administration of drugs or exposure to chemicals the patient should be removed at once from these influences

MALIGNANT NEUTROPENIA (AGRANULOCYTOSIS)

Several thousand cases of this dis ease have occurred since it was first reported in 1922 Most of them have developed on the basis of administra tion of amidopyrine and its various compounds More recently the var ious sulfonamide drugs have been re sponsible for the syndrome Clinical ly the disease shows a wide variety of manifestations but in general it runs a severe rapidly fulminating course the patient soon being over whelmed by various types of infec tious processes because of the loss of cellular resistance

Severe neutropenia is the outstand ing hematologic finding and the red cells and the platelets are seldom af fected The most effective treatment for the typical case of malignant neu tropenia is the use of therapy to con trol infection and penicillin has come to be the treatment of choice The agents used to stimulate the bone marrow have very little value Such agents have included radiation liver extract pentnucleotide and many other products The prognosis

9

The Leukopenic Diseases

Leukopenia is that condition in which the number of circulating leukocytes is below normal without reference to the type of leukocyte involved Thus leukopenia may exist at the expense of the neutrophils in which case it is a neutropenia or if the lymphocytes are decreased it is a lymphocytopenia Since most leukopenic syndromes are caused by a decreased number of neutrophils nearly all patients with leukopenia may develop various secondary bacterial infections because of loss of neutrophilic resistance

Leukopenia may come about because of several mechanisms

1 By simple inhibition of bone marrow output of granulocytes from bacterial toxins etc

2 By arrest of granulocytic maturation usually at the myeloblastic level as seen in aleukemic leukemia

3 By infiltration of the marrow with various tumors as in multiple myeloma or metastatic carcinomatosis

4 By elimination of white cells from the vascular system into large infected areas as into the peritoneal cavity in generalized peritonitis

5 By increased destruction of white cells in peripheral blood Though theoretically possible no clinical example of this is available

6 By redistribution of cells in the vascular system, as seen after the injection of foreign protein or adrenalin

7 By redistribution of white cells throughout the entire body as seen in aleukemic leukemia

In most of the leukopenic states the bone marrow fails to produce a sufficient number of cells This may be because of maturation arrest or damage to the marrow by various toxins drugs and chemicals Certain infectious diseases are characterized by leukopenia which is usually mild with the total cell count being around 3000 cells per cu mm with a low percentage of neutrophils

Leukopenia is commonly observed in the early stages of many infectious diseases such as measles German measles mumps influenza malaria undulant fever and typhus fever and during overwhelming pyogenic infections Leukopenia is also seen in such diseases as histoplasmosis Banti s syndrome and the relapse phases of pernicious anemia in aleukemic leukemia and usually in aplastic or hypoplastic anemias where other elements of the bone marrow show a correspondingly severe depression

Severe leukopenia may also develop because of excessive functional activity of the spleen In such instances the leukocytes are presumably

10

The Iron-deficiency Anemias

(See Plate 16 pp 74 75)

CLASSIFICATION OF ANEMIAS

The most important objective of a laboratory and clinical study in the evaluation of any anemia is to classify it with particular reference to the exact nature of the deficiency

All anemias should be classified into one of four large groups These are as follows

1 Iron-deficiency anemias
2 Deficiency of antianemia factor
3 Hemolytic anemias
4 Anemias of bone marrow damage

If the anemia is not properly classified into one of these four major categories it is practically impossible to treat the condition intelligently The older classification of primary and secondary anemias should be discarded In nearly every instance any anemia can be classified into one of these four groups by carrying out a certain group of laboratory procedures which should include the following Red-cell count white-cell count hemoglobin estimation differential cell count reticulocyte estimation packed-cell volume computation of volume index computation of color index and fragility test in the hemolytic types After these procedures have been carried out it is possible to determine exactly the type of anemia and to place it in one of the four categories mentioned

After preliminary studies it may be necessary to make further determinations depending upon what results are obtained from the original studies The studies outlined above will enable one to classify the anemia into a hematologic classification which is based upon the number of red cells, hemoglobin content of cells and size of cells If the red cells are normal in number such an anemia is said to be normocythemic if the hemoglobin content is normal it is referred to as normochromic and if the average cell size is normal it is then called normocytic If these values are decreased it is referred to by the terms hypocythemic hypochromic and microcytic If these values are increased the corresponding terms are hypercythemic hyperchromic and macrocytic Thus by knowing these three factors—number of red cells average hemoglobin content and average cell size—it is possible to classify any anemia at once by using the terminology described above Some anemias therefore are hypochromic and microcytic others hyperchromic and macrocytic etc.

is much better now since penicillin can be used and nearly all patients recover from the disease

CHRONIC NEUTROPENIA

The syndrome of chronic neutropenia has been described as a condition in which there is a prolonged but moderate decrease in the number of circulating neutrophils below normal It is associated with some weakness fatigue a tendency to tire easily and a predisposition to infections Intramuscular liver extract is probably the best therapeutic agent for this particular syndrome

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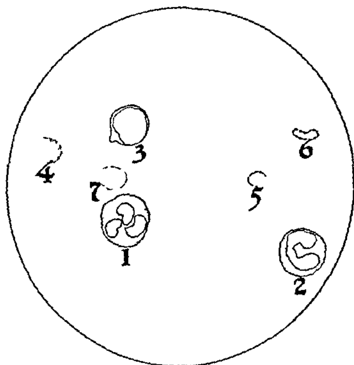
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PLATE 16

MICROCYTIC HYPOCHROMIC ANEMIA

(SECONDARY ANEMIA)

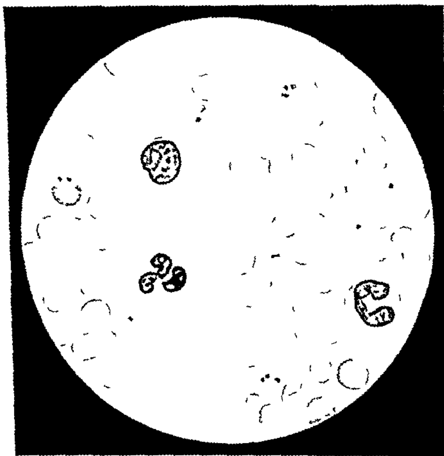


1 Segmented neutrophil
2 Band neutrophil
3 Lymphocyte
4 Erythrocyte with basophilic stippling and polychromasia
5 Microcyte
6 Poikilocyte
7 Normocyte

Blood findings (patient with chronic post hemorrhagic anemia)		Differential		
Hemoglobin	5 Gm (Newcomer's method)	Myelocytes	0%	
R B C	3 000 000 per cu mm	Juveniles	1	
W B C	9 800 per cu mm	Bands	6	
Platelets	500 000 per cu mm	Segmenters	61	
		Total neutrophils		68%
Color index	0.5	Lymphocytes		9 [illegible]
Volume index	0.6	Eosinophils		1 [illegible]
Reticulocytes	6.0	Basophils		1%
		Monocytes		2%

Erythrocytes hypochromic and microcytic with anisocytosis poikilocytosis polychromatophilia and basophilic stippling

PLATE 16



THE IRON DEFICIENCY ANEMIAS

Iron deficiency anemias may develop because of hemorrhages either acute or chronic various nutritional deficiencies pregnancy, various intestinal disorders such as chronic diarrhea and ulcerative colitis, and intestinal parasitism of all types They may be a result of infectious diseases of practically any type if the disease is prolonged, of inadequate diet far advanced malignant tumors and a great many other conditions They comprise well over 90 per cent of all anemic states

This type of anemia is practically always hypochromic and the average red cell does not contain its normal quota of hemoglobin with the color index below one whereas anemias caused by deficiency of antianemia factor are usually macrocytic in type and nearly always hyperchromic with a color index above one

Plate 16 shows a typical example of microcytic hypochromic iron deficiency anemia which in older terminology was referred to as secondary anemia The outstanding characteristic of this group of anemias is the fact that the red cells do not have their normal quota of hemoglobin Microcytosis usually is associated with the hypochromic iron deficiency anemias particularly when the process is a long standing and chronic one The color index *is always low* and the number of red cells may be normal or below normal

A classic hypochromic, microcytic anemia is characterized by microcytic cells showing variable degrees of central pallor within the cells There is also some slight variation in size and in shape of the cells and some of them may show variable degrees of basophilic stippling The platelets and the white cells are usually not altered Such anemias as shown in this plate may develop as a result of an acute hemorrhage involving large amounts of blood chronic blood loss regardless of the cause acute infectious diseases of various types chronic infectious states such as typhoid fever, malaria tuberculosis syphilis prolonged febrile diseases influenza subacute bacterial endocarditis ulcerative colitis and many other similar conditions Such anemias are likely to develop in various types of malignancies and in practically all types of parasitic infestation if the process is sufficiently prolonged It is the classic anemia of malaria and it occurs frequently in pregnant women Furthermore it is the type of anemia resulting from dietary restriction and is seen in hypothyroidism or myxedema It is the anemia described in the older *literature as* seen in chlorosis

A great many people have variable degrees of hypochromic microcytic anemia and it seems unusually prevalent among women being caused by a combination of factors including dietary restriction chronic menstrual blood loss perhaps associated with hidden foci of infection

TREATMENT OF HYPOCHROMIC ANEMIAS

The most important therapeutic measure in any *iron-deficiency* anemia is to discover its cause and remove it if possible The anemia itself

however is the type that responds to the administration of adequate doses of a suitable iron preparation Liver extract providing the hemato poietic factor is not required in this group of anemias

Iron is the most important factor in building the hemoglobin molecule and a well balanced diet contains suf ficient iron for average demands Nearly every case of hypochromic anemia can be corrected by the ad ministration of iron alone without the use of other supplementary met als which are sometimes used as so-called catalytic agents The adminis tration of from 10 to 15 grains of ferrous sulfate daily by mouth is adequate for the correction of prac tically every case of hypochromic anemia The use of copper and other such agents is not indicated Iron has very little value when given by par enteral methods since the amount of iron that can be given by injection is so small that it seems useless Futhermore the reactions are not always favorable Ferrous sulfate should be given three times daily after meals or if it is not well toler ated it can be divided into still smaller doses and given in a larger number of doses during the day

A severe case of hypochromic ane mia usually responds satisfactorily with as much as a 2 per-cent increase in hemoglobin daily and if a 1 per cent daily increase is maintained this is considered to be a satisfactory re sponse During treatment of severe cases there may be an associated mild reticulocytosis as high as 5 per cent following iron therapy Some pa tients show achlorhydria along with their iron deficiency anemia Even though correction of anemia is not followed by correction of the achlor hydria it is not necessary to use hy drochloric acid in the treatment of such patients

Supplementary measures to iron therapy include the use of blood transfusions particularly if the ane mia is quite severe An occasional patient may require one or two trans fusions in the early part of treatment which makes the iron more effective during the later days or weeks of treatment Transfusions are not in dicated however except in unusually severe forms of iron-deficiency ane mias Some believe that a weekly in tramuscular injection of from five to ten units of liver extract is a valu able supplementary measure in the treatment of iron deficiency anemia

THE IRON DEFICIENCY ANEMIAS

Iron-deficiency anemias may develop because of hemorrhages either acute or chronic various nutritional deficiencies, pregnancy various intestinal disorders such as chronic diarrhea and ulcerative colitis, and intestinal parasitism of all types They may be a result of infectious diseases of practically any type if the disease is prolonged of inadequate diet far advanced malignant tumors and a great many other conditions They comprise well over 90 per cent of all anemic states

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TREATMENT OF HYPOCHROMIC ANEMIAS

The most important therapeutic measure in any iron-deficiency anemia is to discover its cause and remove it if possible The anemia itself

the bone marrow is able to compensate for this destruction by increased output of reticulocytes then the patient will not develop anemia It is only when this compensation is broken that the patient is likely to develop the clinical signs of the disease In the meantime however because of accelerated cell destruction the patient may show a subclinical or clinical jaundice which usually has been present for many years Examination usually reveals the presence of the jaundice and an enlarged spleen

Examination of the blood reveals a large number of reticulocytes a classic picture of small intensely stained microspherocytic cells frequently an associated leukocytosis which may even be a leukemoid reaction the presence of excessive amounts of bilirubin in the blood an elevated icterus index and increased amounts of urobilinogen in the urine and urobilin in the stools The cells show increased fragility when placed in hypotonic saline The condition can be cured promptly and permanently by splenectomy After splenectomy the cell values are soon restored to normal reticulocytes decrease in number the spherocytes persist but apparently are able to function as oxygen carriers and are not destroyed in large numbers as before splenectomy Even the increased fragility persists but the patient becomes clinically cured The patient nevertheless is capable of transmitting the disease to his progeny It is sometimes difficult to transfuse these patients because of unfavorable reactions from blood that appears to be perfectly matched so the patient should be watched carefully for evidence of accelerated blood destruction after transfusions

OTHER CAUSES OF HEMOLYTIC ANEMIA

Although congenital hemolytic icterus is the classic type of hemolytic anemia there are many agents and diseases that can cause accelerated destruction of red cells These include certain types of generalized septicemia particularly those caused by hemolytic streptococci Rare hemolytic anemias are seen in syphilis and in severe malaria[7] and cell destruction may be sufficient to give hemoglobinuria or so-called blackwater fever A number of drugs chemicals[8] and poisons including phenylhydrazine acetylphenylhydrazine potassium chlorate sulfonamide drugs phosphorus dinitrophenol saponin ricin snake venom arsenical compounds etc are capable in certain people of causing accelerated blood destruction The type of mass cell destruction following incompatible blood transfusions is also on the same basis On rare occasions patients have auto-agglutinins and autohemolysins in their own blood There are certain clinical entities that are characterized by intravascular cell destruction including sickle cell anemia[6] Lederer s acute hemolytic anemia and the various erythroblastic anemias of childhood such as Cooley s and von Jaksch s anemia The syndrome of newborn infants usually called erythroblastosis foetalis is a severe hemolytic anemia based on incompatibility of the Rh factor between mother and infant.

Various disease syndromes charac

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11

The Hemolytic Anemias

(See Plates 17 18 19, pp 80 83 86 87)

ANEMIA OF CONGENITAL HEMOLYTIC JAUNDICE

(See Plate 17)

The hemolytic anemias are caused by excessive intravascular destruction of red cells When this occurs there is usually adequate bone marrow compensation for the destruction as manifested by excessive production of reticulocytes In this type of anemia it is important to discover the cause of the excessive cellular destruction and it is necessary to study the products of cell destruction, such as bilirubin content of blood plasma and urobilinogen and urobilin in urine and stools Classic examples of this anemia include chronic familial hemolytic anemia acute hemolytic anemia of Lederer certain anemias of syphilis paroxysmal hemoglobinuria anemia of sulfonamide-drug administration anemia of lead poisoning sickle cell anemia hemolytic anemia of the newborn etc

Plate 17 shows the type of blood picture seen in congenital hemolytic icterus which is a classic example of hemolytic anemia This is an inherited familial disease characterized by prolonged attacks of jaundice with variable degrees of anemia and splenomegaly It is a type of true hemolytic anemia which is caused by the destruction of excessive numbers of red cells This cell destruction takes place because a large number of them are inherently defective the defect consisting of an excessive fragility which renders the cells unable to withstand the normal factors of trauma in the vascular system so that they are subsequently destroyed by the spleen in large numbers

The disease is transmitted according to the mendelian law of inheritance It occurs in any race of either sex in practically all countries It occurs in no specific age group but most cases are discovered early in life It is not known why the individual produces the small microspherocytic red cell which is biconvex rather than biconcave is more globular and rounded has a smaller diameter and is no doubt partially hemolyzed and more fragile when placed in hypotonic salt solution The inherited defect whatever its nature causes swelling and sphericity of the cells

In this condition the red cells may be normal or below normal in number The reticulocytes are always elevated sometimes to an astonishing degree and the rate of destruction governs the amount of reticulocytosis If the cells are destroyed in large numbers by the overactive spleen and

PLATE 17

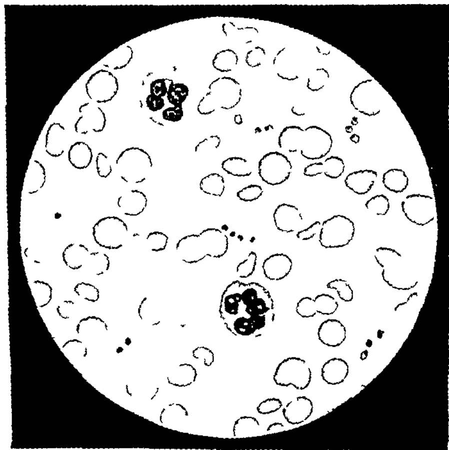
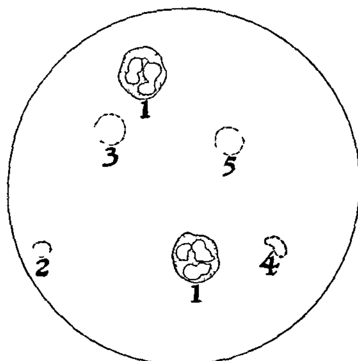


PLATE 17

ANEMIA OF HEMOLYTIC JAUNDICE

(SECONDARY ANEMIA)



1 Neutrophils
2 Microcyte
3 Macrocyte
4 Poikilocyte
5 Polychromatocyte

Blood findings		Differential	
Hemoglobin	7 8 Gm (Newcomer s method)	Myelocytes	0%
R B C	2 600 000 per cu mm	Juveniles	2%
W B C	7 800 per cu mm	Bands	6%
Platelets	306 000 per cu mm	Segmenters	57%
		Total neutrophils	65%
Color index	0 8	Lymphocytes	28%
Volume index	0 7?	Eosinophils	1%
Icterus index	15 0	Basophils	2%
Reticulocytes	13 0%	Monocytes	4%

Fragility of erythrocytes in hypotonic salt solutions Hemolysis beginning at 0 49% NaCl and complete at 0 40%

Erythrocytes microcytic and hypochromic with marked anisocytosis poikilocytosis and polychromatophilia

PLATE 17

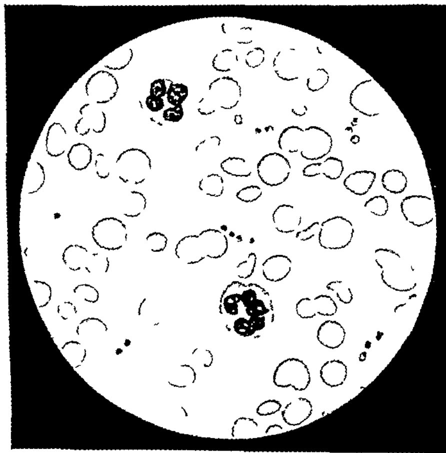
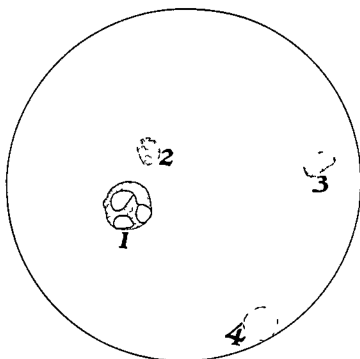


PLATE 18

ANEMIA OF LEAD POISONING
(SECONDARY ANEMIA)

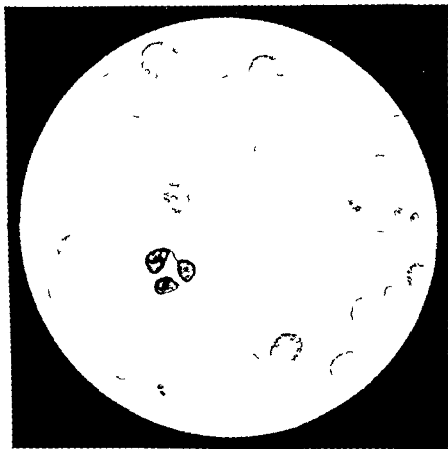


1. Neutrophil
2. Erythrocyte with coarse basophilic stippling
3. Erythrocyte with fine basophilic stippling
4. Polychromatocyte

Blood findings		Differential	
Hemoglobin	6.5 Gm (Newcomer's method)	Myelocytes	0%
R B C	3,150,000 per cu mm	Juveniles	5%
W B C	8,450 per cu mm	Bands	11%
Platelets	295,000 per cu mm	Segmenters	60%
Color index	0.6	Total neutrophils	76%
Volume index	0.8	Lymphocytes	16%
		Eosinophils	2%
		Monocytes	6%

Erythrocytes hypochromic and microcytic with pronounced basophilic stippling

PLATE 18



terized by hemoglobinuria are on the same basis these including cold hemoglobinuria which is probably luetic in origin march hemoglobinuria seen after prolonged muscular exercise following inactivity nocturnal hemoglobinuria in which cell destruction occurs mainly during sleep allergic hemoglobinuria as seen in poisoning in the disease fabismus myoglobinuria etc All these have the same hematologic characteristics in common—massive accelerated cell destruction increased products of cell destruction in the blood urine and stools and compensatory reticulocytosis by the bone marrow An important feature in any hemolytic anemia is to study the patient carefully for exposure to dangerous chemicals or to ingestion of drugs that might be responsible for the condition

ANEMIA OF LEAD POISONING

(See Plate 18)

Plate 18 shows the characteristic blood picture seen in cases where the lead poisoning is severe and of long standing and where the exposure to lead has been considerable This anemia is hemolytic although associated with it *is much evidence of iron deficiency* because of the rather marked hypochromia of the red cells that is *so frequently* seen *Basophilic stippling* may be seen in a *considerable* number of the red cells

Lead poisoning may occur when the metal gains access to the body tissues in excessive quantity whether it be by oral ingestion injection inhalation or skin contact It is frequently seen in industrial workers who are working with lead It is a common finding in paint chippers those who are working in close quarters usually on board ship and it is often seen in house painters It has been reported in infants who gnaw at the paint on their cribs and ingest sufficient lead for poisoning

The outstanding clinical features of the acute form include marked pallor due to the anemia severe abdominal cramps usually constipation and various palsies of the peripheral nerves Furthermore there may be found a blue lead line at the junction of the gums with the teeth *The degree of* anemia is variable and depends upon the amount of lead ingested *and the duration of exposure* The anemia is usually hypochromic the hemoglobin being lower than the *red-cell values There is considerable* achromia usually variable degrees of basophilic stippling some increase in *reticulocytes and frequently some* variation in size and in shape of the red cells If the rate of cell destruction *is severe there will be evidence of* accelerated cell destruction in the blood including an elevated icterus index and urobilinogen in the urine

SICKLE CELL ANEMIA

(See Plate 19)

This *condition* is a true hemolytic anemia which is hereditary and transmissible *according to* the mendelian law It is seen *chiefly* in Negroes but on occasion in white people It is characterized by the presence of crescent shaped or sickle shaped red cells called meniscocytes which are destroyed in excessive numbers in the vascular system and probably in the spleen

The disease occurs in all parts of the world and is practically confined to the Negro race A great many Negroes who do not exhibit the disease clinically show what is referred to as the sickling trait Reliable figures indicate that 7 per cent of all Negroes in the southern United States exhibit the sickling trait but that only 1 out of 15 of these develops the disease clinically It is not known why the red cells have this peculiar deformity but it is known that sickling occurs much more readily in the absence of oxygen and that the amount of sickling varies directly with increased carbon-dioxide content

A typical patient with the disease is a young Negro adult who presents a history of weakness prolonged ill health variable degrees of anemia easy fatigue and other signs referable to anemia Many have disturbances in the intestinal tract including pain nausea and vomiting Some have joint pains and a common finding in cases of long standing is the presence of ulcers on the legs near the ankles There may be slight jaundice The spleen is usually enlarged and easily palpable The diagnosis is readily established by the finding of numerous sickle cells in the blood The total number of red cells is usually low and the hemoglobin lower in proportion with a low color index The reticulocytes are usually increased and the blood may show signs of active marrow regeneration including large numbers of nucleated red cells and a marked leukocytosis The characteristic finding is the sickling of the red cells It is best demonstrated by examining the blood in the wet state obtaining the specimen after a tourniquet has been placed round the finger in order to deplete the oxygen content in the specimen (see page 160)

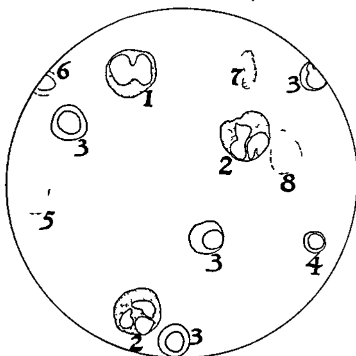
The treatment of sickle-cell anemia is unsuccessful Splenectomy has been given a thorough trial but it apparently is without value Treatment usually consists of multiple transfusions and is largely symptomatic The use of symptomatic therapy and supportive measures during the acute exacerbations of childhood still offer a good prognosis since there is a natural tendency to remission as the patient grows older

OVALOCYTOSIS

Ovalocytosis is that condition in which a variable percentage of the red blood cells are found to be elliptical in shape This too appears to be an inherited anomaly since it has been reported frequently in members of the same family Sometimes as many as 40 per cent of the red cells may be elliptical in the stained smear These cells show no evidence of sickling and the ovalocytosis is not affected by varying degrees of oxygen or carbon-dioxide tension It is seen in either white or colored people and in most patients there is no anemia whatever It is merely an inherited anomaly and apparently is not a disease When the condition is found it should give rise to no particular concern

PLATE 19

SICKLE CELL ANEMIA
(MENISCOCYTOSIS)



1 Juvenile neutrophil
2 Segmented neutrophils
3 Normoblasts
4 Microblast
5 Sickle cell
6 Erythrocyte with Cabot ring body
7 Erythrocyte with basophilic stippling
8 Macrocyte (note endoglobular degeneration)

Blood findings

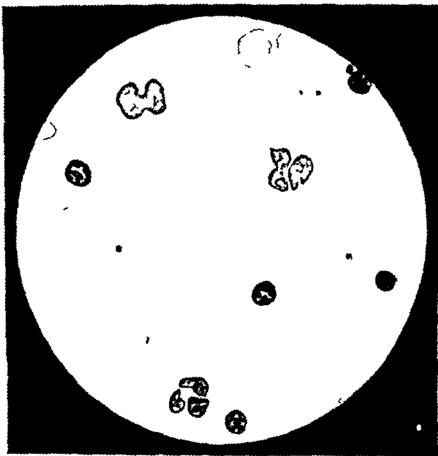
Hemoglobin	7 4 Gm (Newcomer s method)
R B C	2 000 000 per cu mm
W B C	19 000 per cu mm
Platelets	550 000 per cu mm
Color index	1 1
Volume index	1 0
Icterus index	35 0
Reticulocytes	14 0%

Differential

Myelocytes	1%	
Juveniles	8%	
Bands	16%	
Segmenters	60%	
Total neutrophils		85%
Lymphocytes		6%
Eosinophils		2%
Basophils		3%
Monocytes		4%

Erythrocytes slightly hyperchromic with marked anisocytosis polychromatophilia numerous macrocytes sickle cells and normoblasts Wet preparation shows sickling phenomenon in 40 of erythrocytes

PLATE 19



12

Anemias of Marrow Damage

(See Plate 20 pp 90 91)

In anemias of bone marrow damage the classic picture is usually one of reduction of all cellular elements produced in the marrow These anemias have variable degrees of red cell depletion with corresponding hemoglobin loss thrombocytopenia and neutropenia Bone marrow studies are very valuable in confirming an anemia as being in this group

Aplastic anemia is the term applied to a group of anemias characterized by a partial or total inhibition of bone marrow output resulting in severe anemia neutropenia and thrombocytopenia this being followed by a progressively declining course and fatal outcome in most patients The term aplastic anemia implies that the bone marrow is nonfunctional to the point where it no longer is able to supply the requisite number of cells to the peripheral blood Some of these patients show hypoplasia or hypoplastic anemia in which the bone marrow has lost only a part of its function and still continues to supply adequate numbers of cells in one or more of the three cellular series produced in that organ

Aplastic anemia may be divided into two large groups 1 Secondary aplastic anemia that is that group of bone marrow aplasias in which an etiologic agent can be demon 2 Primary idiopathic aplastic a

SECONDARY APLAST ANEMIA

This condition can be cau exposure of the marrow to that are known to be capable o aging that organ Notable these is benzene Benzene m aplasia has been reported in trial workers exposed to that ical in the course of their wo can produce marrow aplasia w is inhaled ingested by mouth jected into the tissues It is th chemical with which aplastic a can be consistently produced experimental animal Marrow a has been reported in indiv working in the dyeing and cle industry when benzene and zene like solvents are used in work The time of exposure t toxic agent is variable

Among other agents capab producing hypoplasia or aplasia marrow are the arsenical pre tions as indicated by the rare d opment of aplastic anemia from use in the treatment of syphilis radiation either from radium roentgen rays is capable of pro ing severe marrow aplasia This

be found in people who have handled radioactive materials or who have been exposed to roentgen rays without adequate protection The important point in any case of aplastic anemia is to take a careful history and determine whether or not the patient has been exposed to or has ingested any of the above named agents A partial inhibition of marrow output is seen in an occasional elderly person Its cause is unknown but it has been attributed to physiologic aging of the marrow Treatment is not effective and the patients are usually supported by transfusions until they succumb from some complication

PRIMARY IDIOPATHIC APLASTIC ANEMIA

This is a disease entity of unknown cause occurring mainly in young adults It is characterized by anemia neutropenia thrombocytopenia and the complications that result from these cellular deficiencies The clinical findings in aplastic anemia depend to a large extent upon the degree of bone marrow depression Usually there is a history of insidious development of pallor weakness and fatigue Some patients may show a syndrome of hemorrhagic disorders because of the thrombocytopenia Others may become overwhelmed by various infectious complications because of their neutropenia The hematologic findings are fairly characteristic since there is always a variable degree of anemia which in some cases may be quite severe with the hemoglobin reduced in proportion and there are also severe granulocytopenia and thrombocytopenia

The blood picture does not show any outstanding characteristic that enables the diagnosis to be made except a decrease of thrombocytes granulocytes and erythrocytes The anemia is usually normochromic and the red cells are usually normal in size On the stained film the red cells may appear to be surrounded by a thin barely pink staining zone of material as seen in Plate 20 The diagnosis can readily be confirmed by aspiration of sternal bone marrow in which there will be found to be an aplasia of all cellular elements and in some instances considerable fat-cell replacement of hematopoietic tissue

Treatment of all marrow aplasias includes the removal of the patient from the offending agent if the agent can be discovered If not the treatment is only palliative usually in the form of large numbers of blood transfusions Frequently the marrow is so aplastic and its cellular output so low that the patient literally has to live on borrowed blood in the form of transfusions With nearly all cases the outlook is hopeless unless something happens to restore the marrow to its normal function As yet there is no specific agent that seems to be capable of doing this

OSTEOSCLEROTIC ANEMIA

Another type of aplastic anemia has been called marble bone disease or osteosclerotic anemia This disease is caused by thickening of the cortical layers of the various bones with encroachment on the marrow cavity In some instances there is complete obliteration of the medullary cavity There is no effective treatment

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Anemias of Marrow Damage

(See Plate 20 pp 90 91)

In anemias of bone marrow damage the classic picture is usually one of *reduction of all cellular elements* produced in the marrow These anemias have variable degrees of red cell depletion with corresponding hemoglobin loss thrombocytopenia *and neutropenia Bone marrow stud*ies are very valuable in confirming an anemia as being in this group

Aplastic anemia is the term applied to a group of anemias characterized by a partial or total inhibition of bone marrow output resulting in severe anemia neutropenia and thrombocytopenia this being followed by a *progressively declining* course and fatal outcome in most patients The term aplastic anemia implies that the bone marrow is nonfunctional to the *point where it no longer is able to* supply the requisite number of cells to the peripheral blood Some of these patients show hypoplasia or hypoplastic anemia *in which the bone* marrow has lost only a part of its function and still continues to supply adequate numbers of cells in one or more *of the three cellular series pro*duced in that organ

Aplastic anemia may be divided into two large groups 1 Secondary aplastic anemia that is that group of bone marrow aplasias in which an etiologic agent can be demonstrated 2 Primary idiopathic aplastic anemia

SECONDARY APLASTIC ANEMIA

This condition can be caused by exposure of the marrow to agents *that are known to be capable of dam*aging that organ Notable among these is benzene Benzene marrow[1] aplasia has been reported in industrial workers exposed to that chemical in the course of their work It can produce marrow aplasia when it is inhaled ingested by mouth or injected into the tissues *It is the only chemical with which aplastic anemia* can be consistently produced in the experimental animal Marrow aplasia has been reported *in individuals working in the dyeing and cleaning* industry when benzene and benzene like solvents are used in their work The time of exposure to the *toxic agent is variable*

Among other agents capable of producing hypoplasia or aplasia of the marrow are the arsenical preparations *as indicated by the rare devel*opment of aplastic anemia from their use in the treatment of syphilis Also radiation either from radium or *roentgen rays is capable of produc*ing severe marrow aplasia This may

PLATE 70

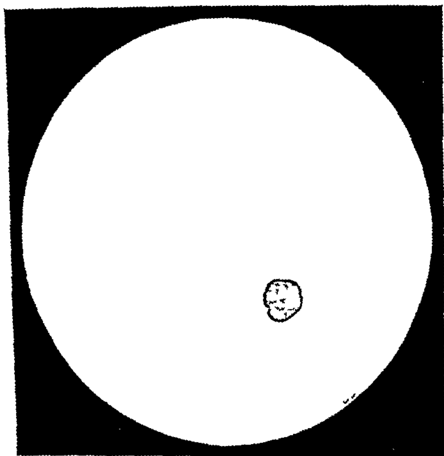
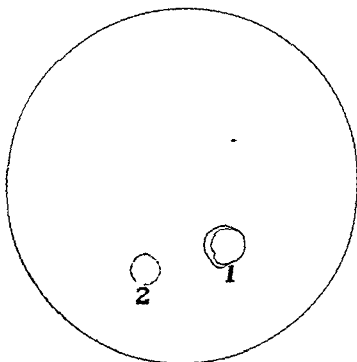


PLATE 20

APLASTIC ANEMIA



1 Lymphocyte
2 Normocyte

Blood findings

Hemoglobin	3 Gm (Newcomer's method)	Differential	
R B C	900 000 per cu mm	Neutrophils	6%
W B C	1 650 per cu mm	Lymphocytes	94%
Platelets	8 000 per cu mm		
Color index	1 0		
Volume index	1 0		
Reticulocytes	None		

Erythrocytes normocytic and normochromic
Note absence of platelets and characteristic halo round red cells

is well over a year before the patient usually consults a physician The symptoms are referable to three major systems—the gastro-intestinal, the neurologic and the hematologic The usual diagnostic triad is weakness sore tongue and numbness and tingling of the extremities The blood findings in pernicious anemia are fairly characteristic with an extremely low red-cell count but the hemoglobin is not reduced in proportion and the color index therefore is above one Many of the cells are macrocytes resulting in a macrocytic, hyperchromic anemia The blood picture shows considerable variation in the size the shape and the staining quality of the red cells referred to as anisocytosis poikilocytosis and polychromatophilia respectively Megaloblasts are sometimes seen in the blood The leukocyte count is usually low the decrease being at the expense of the neutrophils Hypersegmentation of neutrophilic leukocytes has been reported as one of the characteristics of the blood There is always gastric achlorhydria or gastric achylia even with histamine stimulation

The diagnosis of pernicious anemia is usually based on the development of pallor fatigue weakness sore tongue glossitis gastro-intestinal complaints various neurologic findings total achylia of the stomach and the hematologic findings of anemia macrocytosis hyperchromia and increased color and volume indices

Treatment

Treatment of pernicious anemia consists of the administration of the antianemia factor or so-called hematopoietic principle in adequate amounts to restore the hematologic values to normal and after that the use of this principle in adequate amount to maintain the blood values at normal This is usually done by the injection of liver extract daily over a period of approximately two weeks from 15 to 20 units being used at each dose Then the interval between injections is increased gradually until finally the patient can be successfully maintained on a single injection of potent liver extract once every three to four weeks

The use of liver preparations by mouth is hardly worth while A new effective agent in the treatment of pernicious anemia and other macrocytic anemias is the oral administration of vitamin M complex (L casei factor) (folic acid) in as small amounts as ten milligrams per day This agent seems to be equally as effective as injectable liver preparations in the treatment of the disease and maintenance of remissions Adequate treatment is followed by a reticulocytosis beginning about the third or fourth day which may reach a peak as high as from 30 to 40 per cent and continue until the hematologic values return to normal Such a reticulocytosis is shown in Plate 22

OTHER MACROCYTIC ANEMIAS

Similar types of blood pictures may be found in the macrocytic anemias of sprue pellagra certain anemias of pregnancy various gastro-intestinal dysfunctions anemias of widespread liver damage tropical macrocytic anemia occasionally in leukemia and in the disease achrestic anemia in

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The Macrocytic Anemias

(See Plates 21 and 22 pp 94 97)

PERNICIOUS ANEMIA

Macrocytic anemias develop because of a deficiency of the antianemia factor and are seen frequently in pregnancy, pernicious anemia carcinoma of the stomach far advanced liver disease certain forms of tropical anemia sprue and pellagra because of faulty absorption of the antianemia factor and probably others This type responds to treatment with the specific factor in the form of liver extract

Pernicious anemia is a disease of unknown etiology characterized by achlorhydria variable gastro intestinal and neurologic disturbances and a classic type of anemia resulting from dysfunction of erythropoiesis because of a lack of the hematopoietic factor and by periods of spontaneous remission and relapse It is a fatal disease unless treated with specific antianemia factor in the form of liver liver extract stomach preparations etc

The immediate cause of pernicious anemia seems to be a lack of the hematopoietic principle reaching the bone marrow Therefore the basic pathologic finding is an arrest of the normal maturation pattern of red cells in the marrow at the megaloblastic level Even though maturation proceeds from that level the resulting cell discharged into the blood is usually a large macrocyte well filled with hemoglobin

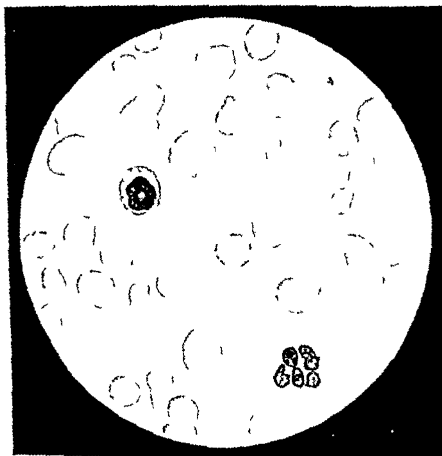
It is known that the hematopoietic factor is formed by interaction between the extrinsic factor in the diet and the intrinsic factor produced by the glands of the normal stomach and the upper duodenum The union of these results in the antianemia factor which is then absorbed stored in the liver and other tissues and released by these tissues as needed and utilized by the bone marrow in sufficient amount to maintain orderly maturation of red cells In view of this pernicious anemia seems to be a disease resulting from a deficiency of the intrinsic factor in the stomach It is therefore primarily a disease of the gastro intestinal tract

The disease occurs mainly in white people of the blond or Nordic types It usually appears first in late adult life or in old age It is thought not to occur in children and rarely in the Negro It predominates in males There is some evidence to indicate a family predisposition to the disease

Symptoms

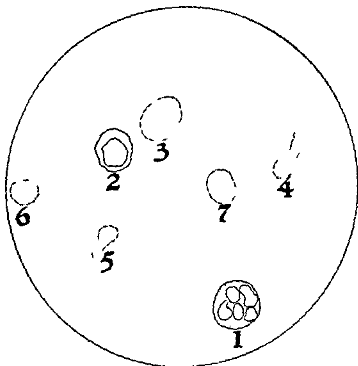
The average duration of symptoms

PLATE 21



PERNICIOUS ANEMIA IN RELAPSE

(PRIMARY ANEMIA)



1 Hypersegmented neutrophil
2 Megaloblast
3 Macrocyte
4 Tailed erythrocyte
5 Racquet erythrocyte
6 Erythrocyte with Howell Jolly bodies
7 Polychromatocyte

Blood findings

Hemoglobin	5 8 Gm (Newcomer s method)	
R B C	1 100 000 per cu mm	
W B C	3 000 per cu mm	
Platelets	40 000 per cu mm	
Color index	1 5	
Volume index	1 4	
Icterus index	12 0	
Reticulocytes	0 1	

Differential

Segmenters	49%
(15% hypersegmented)	
Lymphocytes	50
Eosinophils	1

Fragility of erythrocytes in hypotonic salt solutions Hemolysis beginning at 0 38% NaCl and complete at 0 30

Gastric analysis—achylia

Erythrocytes macrocytic and hyperchromic with marked poikilocytosis moderate polychromatophilia marked anisocytosis occasional Howell Jolly body and pronounced megaloblastemia

PLATE 22

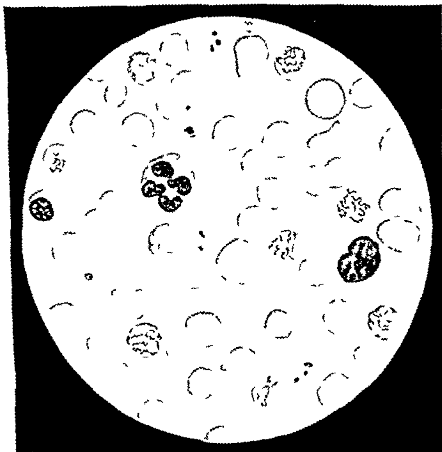
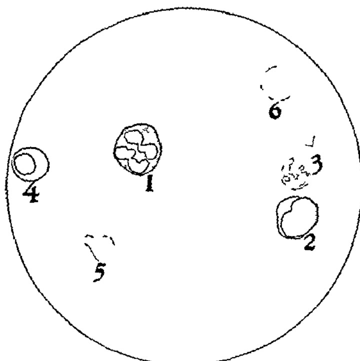


PLATE 22

PERNICIOUS ANEMIA DURING REGENERATION



1 Neutrophil
2 Lymphocyte
3 Reticulocyte
4 Normoblast
5 Poikilocyte
6 Macrocyte (polychromatophilic)

Blood findings (same case as shown in plate 24 during regeneration following liver therapy)

Hemoglobin	12.6 Gm (Newcomer's method)
R B C	3 400 000 per cu mm
W B C	9 600 per cu mm
Platelets	50 000 per cu mm
Color index	1.1
Volume index	1.0
Icterus index	7.0
Reticulocytes	39.0

Differential

Neutrophils	66%
Lymphocytes	40%
Eosinophils	4%

Erythrocytes slightly hyperchromic and normocytic with anisocytosis slight poikilocytosis *polychromatophilia occasional normoblast and marked reticulocytosis*

Gastric analysis—achylia

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The Leukemias

(See Plates 23 24 25 26 27 28 pp 102 105 108 111 114 117)

Leukemia is a progressively fatal disease It is characterized by wide spread hyperplasia of the hematopoietic tissues which results in the production of excessive numbers of immature white blood cells These either circulate in the blood stream or become deposited in the fixed tis sues or both There are three forms of leukemia depending upon the hematopoietic tissue involved These include the myelogenous the lymph atic and the monocytic types On rare occasions a plasma cell type and a megakaryocytic type have been re ported

Leukemia is widely distributed throughout the entire animal king dom It has been reported in chick ens mice pigs horses cattle birds and dogs It occurs spontaneously in these animals and there is little to distinguish it from the disease seen in man Leukemia has also been studied widely in fowls where it has been transmitted from one fowl to another of the same species by the use of cell free material the causative substance therefore being a filter passing agent Fortunately leukemia is rare in the human Males appear to be affected more frequently than females the ratio being about three to one There seems to be no racial susceptibility The disease in its chronic form is rare in childhood but the acute forms are far more common in childhood Chronic leukemia is a disease of mid dle life but it also occurs in the aged It occurs with equal frequency in rich and in poor alike There is no indication that occupation plays any role in its development There is lit tle to indicate a familial tendency in leukemia although in rare instances two cases have been reported in the same family There is nothing to sug gest that the disease is either con genital or inherited A question of some practical importance is the possibility of trauma contributing to the development of leukemia but there has never been ample evidence to justify the correctness of such an as sumption Most evidence indicates that leukemia in all its forms is neoplastic in nature Thus it grows un controlled it establishes secondary metastatic foci and it terminates fa tally with cachexia The cells are of the neoplastic type and there is no indication of a bacterial etiology The most acceptable view is that leukemia is a form of malignancy of the blood forming tissues In both chronic and acute forms of leukemia the process is one of widespread and uncon trolled maturation of the hemato-

which apparently the bone marrow is unable to utilize the hematopoietic principle even though it may be present in adequate amounts These conditions usually do not respond satisfactorily to the administration of the antianemia factor in the form of liver extract

Supplementary treatment of the macrocytic anemias includes the use of blood transfusions when indicated the use of iron preparations if there is a co-existing hypochromia and other symptomatic treatment such as vitamin B complex and a high protein diet

in the circulating blood with infiltration of these cells into the various tissues. This form of leukemia is rarely seen before adult life; it is chiefly a disease of middle age.

Symptoms and Physical Findings

The onset of the disease is insidious. Early symptoms are usually caused by slowly developing anemia and include fatigue, weakness, and increasing pallor. In some patients the first sign may be a large spleen with a sense of fullness and pressure in the abdomen. If not seen till late stages, there will be extreme fatigue and pallor, usually accompanied by a febrile course. First symptoms may be those suggestive of an inflammatory process or of abdominal or cardiac disease. Some symptoms may suggest bone or joint disease, and then some are seen with skin changes the outstanding features. If the platelets are decreased, the original symptoms may be those of hemorrhage.

The physical findings are variable. The skin is pale because of anemia and there may be purpuric spots over the body. A large hard spleen is usually found. In some cases this extends as low as the crest of the ilium. A systolic murmur may be present because of anemia, and there may be generalized lymphadenopathy involving the superficial groups of glands. Tenderness in the bones is a common finding.

Blood findings in chronic myelogenous leukemia are usually quite characteristic. The leukocytes are usually tremendously elevated in number, sometimes as high as 300,000 or 400,000 cells per cu. mm., and the red cells are usually depleted in number. Occasionally the leukocyte count may exceed the red-cell count in far advanced cases. A study of the cellular pattern of the leukocytes shows a marked degree of cellular immaturity which is manifested by the appearance of all types of cells in the granulocytic series ranging from myeloblasts to fully segmented neutrophils. In general, the greater the number of immature cells, the more acute the leukemic process will be in its clinical course. If the blood picture includes large numbers of such immature cells as eosinophilic, neutrophilic, and basophilic myelocytes, this is said to be a bad prognostic omen. If at any time the cellular picture shifts toward greater immaturity, this indicates a fairly early termination of the illness. The typical picture of chronic myelogenous leukemia is shown in Plate 23 and the same blood is shown stained with peroxidase stain in Plate 24.

Treatment

The treatment of chronic myelogenous leukemia is concerned mainly with the judicious use of radiation and perhaps arsenic. It is agreed that radiation therapy probably does not prolong life, but it does reduce the number of circulating leukocytes, reduces the size of the spleen—sometimes to a normal level—and certainly makes the patient more comfortable. Arsenic is a valuable agent and it can be used in the form of Fowler's solution beginning with two or three drops daily and increasing by one drop daily until the point of tolerance is reached. It is a valuable preparation to use between the times when radiation is employed.

poietic tissues and when these neoplastic blood cells are discharged into the circulation either they continue to circulate or they become rapidly deposited in fixed tissues Therefore the total number of leukemic cells in the blood varies considerably In some patients the white cell count is extremely high in others the total cell count may be below the normal level Such instances are referred to as aleukemic leukemia or the aleukemic phase of leukemia

EXPERIMENTAL PRODUCTION OF LEUKEMIA

Many efforts have been made to produce the disease in a lower animal by the injection of indole in mice the injection of tar into the marrow of young white rats the injection of benzene into mice the feeding of benzene into mice and rats and the exposure of animals to radium and roentgen rays In no instance have the attempts been uniformly successful although there are occasional reports of the development of leukemic like processes as a result of some of these procedures Leukemic blood from the human has been injected into normal individuals with no development of the disease Many efforts have been made to transfer it from the human into monkeys dogs rabbits and other lower animals but without success The transmissible type of fowl leukemia previously referred to is the single outstanding example of consistent successful transmission of leukemia from one animal to another

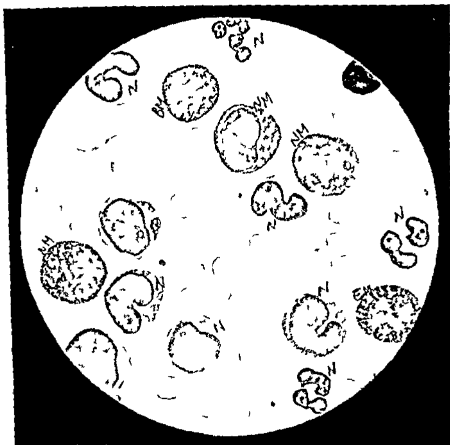
Leukemia can be transmitted between mice of the same strain by the transmission of living leukemic cells in the inoculum In general leukemia progresses without exception to a fatal termination

Many agents have been used for its treatment Treatment of the chronic forms of leukemia has been fairly successful in that the disease is held in abeyance for brief periods of time particularly by the use of roentgen radiation and more recently by the use of radioactive materials such as radioactive phosphorus No type of treatment has proved to be effective in acute leukemia All these patients die without exception All patients with leukemia are supported mainly by blood transfusions Many of them receive injections of liver extract large amounts of iron vitamin preparations of one type or another and radiation therapy to the affected spleen lymph glands and other areas that show evidence of being invaded by leukemic cells The duration of life expectancy in the leukemic processes varies with the type of leukemia In the chronic forms the life expectancy is usually from one to four or five years while in the acute forms it is usually only a few months at the best It would appear that a successful treatment for leukemia will not be developed until a successful treatment for malignancies in general is available

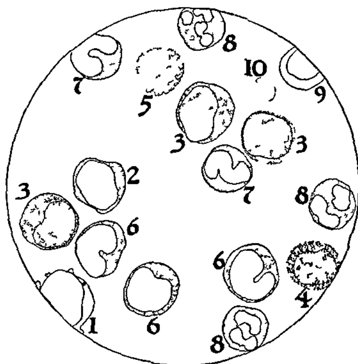
CHRONIC MYELOGENOUS LEUKEMIA (See Plates 23 and 24)

Chronic myelogenous leukemia is a fatal disease characterized by marked hyperplasia of the granulocytic elements of the bone marrow and usually by high numbers of leukocytes

PLATE 23



CHRONIC MYELOID LEUKEMIA



1 Myeloblast
2 Premyelocyte
3 *Neutrophilic myelocytes*
4 Eosinophilic myelocyte
5 Basophilic myelocyte
6 Juvenile neutrophils
7 Band neutrophils
8 Segmented neutrophils
9 Macroblast
10 Poikilocyte

Blood findings

Hemoglobin	10 1 Gm	(Newcomer s method)
R B C		3 050 000 per cu mm
W B C		270 000 *per cu mm*
Platelets		190 000 per cu mm
Color index	1 0	
Volume index	0 9	
Reticulocytes	12 0%	

Differential

Myeloblasts	2%
Premyelocytes	2%
Neutrophilic myelocytes	*18%*
Eosinophilic myelocytes	8%
Basophilic myelocytes	4%
Juvenile neutrophils	19%
Band neutrophils	21%
Segmented neutrophils	22%
Lymphocytes	1%
Eosinophils	2%
Basophils	1%
Monocytes	0%

Erythrocytes normochromic and slightly microcytic with poikilocytosis anisocytosis polychromatophilia and occasional normoblast and macroblast

PLATE 24

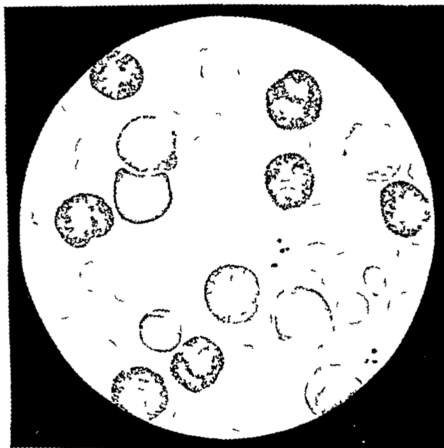
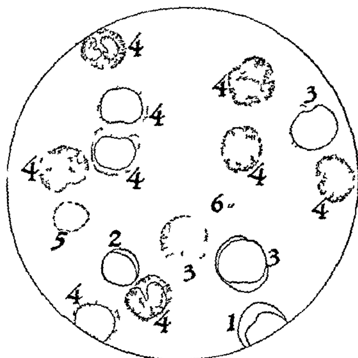


PLATE 24

CHRONIC MYELOID LEUKEMIA

(PEROXIDASE STAIN)



1 Nongranular myeloblast
2 Nongranular cell (either a lymphocyte or a micromyeloblast)
3 Faintly granular cells (typical reaction of premyelocytes)
4 Heavily granulated myeloid cells (myelocytes, juveniles, bands and segmenters)
5 Erythrocyte
6 Cluster of platelets

This plate represents a peroxidase stain of the case shown in Plate 23. A differential count shows 97% peroxidase-positive granular cells and 3% of the nongranular types.

and weakness generalized lymphadenopathy and the presence of large numbers of lymphocytes in the blood It has to be differentiated from any cause of lymphadenopathy including glandular tuberculosis Hodgkin s disease inflammatory lymphadenitis lymphosarcoma syphilis infectious mononucleosis etc The marked lymphocytosis has to be differentiated from that seen in whooping cough and occasionally in tuberculosis There may be aleukemic phases in chronic lymphatic leukemia

Treatment

The treatment is usually the judicious employment of roentgen ray directed toward the masses of enlarged lymph glands and spleen Fowler s solution can also be used between periods of radiation treatment The disease is progressive and extends over a period of some three or four years but a fatal termination is inevitable

MONOCYTIC LEUKEMIA

(See Plate 26)

Monocytic leukemia may occur in chronic subacute or acute forms Because of the controversy over the origin of monocytes some of these cases have been designated as leukemic reticulo-endotheliosis and others as monocytoid forms of myelogenous leukemia This type of leukemia occurs infrequently since not more than some two hundred cases have been reported in medical literature The onset of this disease is usually more sudden than the lymphatic and the myelogenous types There may be a fairly rapid development of severe anemia associated with a hemorrhagic syndrome or there may be an acute febrile attack Sepsis of the oral tissues and bleeding from the gums are frequent findings in monocytic leukemia The usual symptoms are fever sore throat glandular enlargement pain in the joints weight loss purpura and occasionally jaundice Patients with monocytic leukemia are usually more acutely ill than those with the lymphatic and the myelogenous types There is usually a palpable spleen Many of these patients first consult a dentist because of bleeding gums and gingivitis

The blood findings are quite characteristic, since there is usually an increased number of monocytes which may be as high as from 200 000 to 300 000 cells per cu mm., but there are also aleukemic phases There is a predominance of cells designated as monocytes and occasionally there may be considerable numbers of monoblasts The degree of anemia is variable and the platelets are usually reduced in number resulting in a hemorrhagic state The life expectancy is considerably less than in lymphatic and in myelogenous leukemia since the disease usually runs its course in a few months Occasionally a patient may be seen with what appears to be monocytic leukemia but in reality it is the myelogenous type

Treatment

Treatment is of little value in this form of leukemia If it is characterized by sufficient chronicity radiation treatment may be employed especially if the patient has considerable enlargement of the superficial

Radiation directed to the enlarged spleen and glands is the most popular type of treatment

In occasional instances chronic myelogenous leukemia will not run its course in a short time and the patient will live for a great many years The average duration of life after diagnosis however is from about three to four years During this time the patient remains in a fairly good state of health carrying on his usual normal activities Even though the leukemic patient may be unusually susceptible to intercurrent infections when this does happen the infection itself seems to exert a beneficial influence on the disease process in that a wildly disordered cellular pattern may apparently be brought under control for a brief period during the course of the infectious disease

CHRONIC LYMPHATIC LEUKEMIA (See Plate 25)

This type of leukemia is also fatal It is characterized by widespread hyperplasia of the lymphoid tissues accompanied by generalized lymphadenopathy of both superficial and deep gland groups and by increased numbers of lymphocytes in the blood and their deposition in the various tissues This form of leukemia occurs in middle and late life and predominates in the male It accounts for about 20 per cent of all cases of leukemia

Symptoms and Physical Findings

The disease has an insidious onset The first signs may be weakness fatigue and pallor and some patients note the painless enlargement of cervical lymph glands as the first sign In the far advanced cases the symptoms may be those referable to anemia Examination usually reveals a marked pallor of the skin and the mucous membranes general glandular enlargement of all superficial groups of lymph nodes including servical axillary and inguinal glands The glands vary from small ones barely palpable to very massive enlargement several centimeters in diameter They are usually freely movable and not attached to the skin The spleen is also enlarged in chronic lymphatic leukemia but not to the extent usually seen in the myelogenous type In this as in other leukemias there may be some enlargement of the liver probably caused by cell infiltrations

Blood findings in chronic lymphatic leukemia present little difficulty in diagnosis The leukocyte count usually reaches a high level and the predominating cells are small adult lymphocytes mixed with fewer numbers of large lymphocytes Lymphocytic cells may comprise as many as 99 per cent of all white cells Along with the lymphocytes are large numbers of so called basket cells also called smudge cells This same type of smudge cell is seen also in other forms of leukemia The red cells are usually depleted in number depending upon the extent of the anemia Platelets may also be reduced in number but this does not happen to the extent seen in myelogenous leukemia nor as frequently The basal metabolic rate is usually high in lymphatic leukemia

The diagnosis of chronic lymphatic leukemia is based usually on slowly developing anemia fatigue

PLATE 25

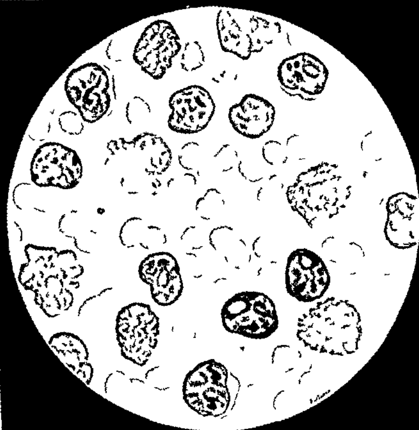
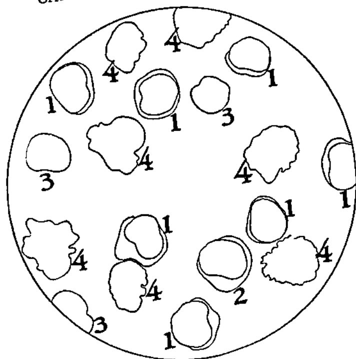


PLATE 25

CHRONIC LYMPHATIC LEUKEMIA



1 Lymphocytes
2 Lymphocyte with azure granules
3 Nuclei without cytoplasm
4 Smudges (degenerating lymphocytes)

Blood findings

Hemoglobin	8 4 Gm (Newcomer s method)
R B C	3 700 000 per cu mm
W B C	390 000 per cu mm
Platelets	245 000 per cu mm
Color index	0 6
Volume index	0 7
Reticulocytes	3 5%

Erythrocytes hypochromic and microcytic

Differential

Large lymphocytes	6%
Small lymphocytes	92%
Segmented neutrophils	2%
Numerous smudge forms	

Peroxidase reaction

Granular cells	2%
Nongranular cells	98%

PLATE 76














PLATE 26

SUBACUTE MONOCYTIC LEUKEMIA

(MONOCYTOID MYELOGENOUS LEUKEMIA)



1



2



3



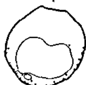
4



5



6



7



8



9



10



11



12

The cells in this plate were drawn from a case of leukemia designated as the monocytic type based upon the predominating cells in the blood samples of which are shown on this plate These cells presented characteristics of monocytes in both the stained smear and supravital reactions This patient finally died with a blood picture and autopsy findings of typical myelogenous leukemia Cells 1 2 and 3 are smaller forms of monocytic cells showing the characteristic folding lobulated irregular nuclei with variations in cytoplasmic color and granulation Cells 4 5 and 6 are larger forms of similar cells Cell 4 shows one large nucleolus and two smaller ones Cell 5 shows a single large nucleolus and cell 7 is a heavily granulated monocytic cell with one large nucleolus and one smaller one Cell 8 shows some nuclear fragmentation and a single nucleolus Cells 9 10 11 and 12 show further variations of the predominating leukemic cells

derness over the sternum and other bones Some patients show signs of meningeal irritation

Blood Findings

As seen in Plates 27 and 28 the blood findings depend on the type of leukoblast predominant in the peripheral blood Since most of the patients apparently have the myeloblastic type the usual blood picture will be that of large numbers of myeloblasts in the blood Myeloblasts may be large middle sized or small giving rise to the terms macromyeloblast normomyeloblast and micromyeloblast (see Plate 4)

The myeloblast is a cell that it is sometimes difficult to recognize with certainty and the smaller forms are frequently confused with small lymphocytes This difficulty of identifying myeloblasts especially in cases where the total cell count is low frequently results in an erroneous diagnosis and the true condition may go unrecognized for considerable periods of time There is usually a rather marked anemia which in some cases may be quite profound

The diagnosis of acute leukemia is based upon the presence of substantial numbers of leukoblasts particularly myeloblasts in the blood stream and confirmatory evidence is secured by the examination of bone marrow in which the marrow is found to be crowded with leukoblastic cells with diminuation of erythropoietic tissues.

Acute leukemia may be confused with various types of sepsis purpura hemorrhagica stomatitis Vincent s infection diphtheria agranulocytosis tuberculosis Hodgkin s disease and any other acute febrile illness

Treatment

Treatment of acute leukemia is entirely unsatisfactory There is no agent as yet employed that seems to affect the course of the disease The usual treatment consists of repeated transfusions although it is done with a sense of futility in the knowledge that it is prolonging the patient s life only a short time at best Radiation apparently is entirely without effect and actually is contraindicated since the patients frequently have severe reactions Radioactive phosphorus has been used in acute leukemias but without any success whatever

lymph glands or spleen If radiation treatment is employed it should be done with considerable caution and very small doses should be used Fowler s solution and the use of multiple transfusions are other measures that are helpful

THE ACUTE LEUKEMIAS

(See Plates 27 and 28)

Acute leukemia is a rapidly fatal malady of unknown cause It is characterized usually by a sudden onset a febrile course considerable ulceration of the oral tissues multiple hemorrhages from skin and mucous membranes the development of a severe anemia the presence of considerable numbers of immature leukoblasts in the blood stream infiltration of the various organs with these cells a progressive course unaffected by treatment and death in every case There is little to be gained in knowing whether acute leukemia is myelogenous lymphatic or monocytic except that the question is one of academic interest The types of acute leukemia include acute myeloblastic leukemia acute lymphatic leukemia and acute monocytic leukemia Some writers refer to the entire group as acute leucoses which is just as well

The acute leukemias comprise about one third of all leukemias The disease is rare in adults especially in later life and most cases occur in children and in young adults However the disease may be seen in middle life It predominates in males in a ratio of two to one It is seen in all races and has no peculiar geographic or occupational incidence Some have suspected that the acute leukemias may be infectious in origin because of the sudden onset out of full health the rather active febrile course and the periods of leukopenia that frequently alternate with the leukocythemia However no organism has been isolated that would tend to confirm this The acute leukemias show marked hyperplasia of the hematopoietic tissues involved In the myelogenous form the bone marrow is crowded with myeloblasts and apparently the cells are unable to mature beyond that level They then are poured into the blood stream in large numbers and are deposited in various tissues throughout the body

Symptoms

The onset of symptoms may be sudden or gradual Sometimes preceding infectious states such as respiratory diseases sore throat and gastro-intestinal upsets may appear to initiate the process One never knows however whether the leukemia was present before these episodes developed Common early signs are ulcerations of the mouth bleeding gums various hemorrhages from a variety of sources extreme weakness marked pallor profound anemia and a febrile course There may or may not be enlargement of the lymph glands and the spleen may or may not be palpable A common onset in children is that of cervical lymphadenopathy a mild febrile course over a period of some weeks during which time possible Hodgkin s disease lymphosarcoma infectious mononucleosis tuberculosis or simple lymphadenitis are usually suspected The patient usually has a systolic hemic murmur and some ten

PLATE 77

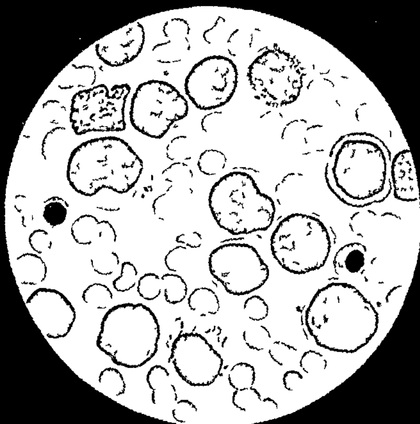
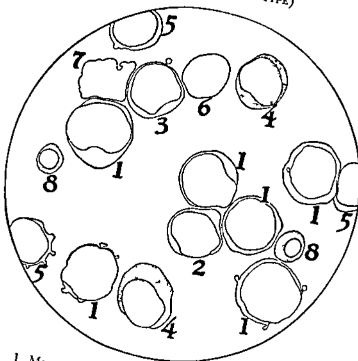


PLATE 27

ACUTE MYELOID LEUKEMIA

(MACROMYELOBLASTIC TYPE)



1 Macromyeloblasts
2 Normomyeloblast
3 Normomyeloblast with Auer bodies in cytoplasm
4 Neutrophilic myelocytes (young)
5 Micromyeloblasts
6 Myeloblastic nucleus without cytoplasm
7 Smudge (degenerating myeloblast)
8 Normoblasts with basophilic stippling in cytoplasm

Blood findings

Hemoglobin	4 7 Gm (Newcomer's method)
R B C	1 450 000 per cu mm
W B C	105 000 per cu mm
Platelets	74 000 per cu mm
Color index	1 0
Volume index	0 7
Reticulocytes	15 0%

Differential

Myeloblasts	90
Premyelocytes	7
Myelocytes	3

Peroxidase reaction

Nongranular cells	85
Granular cells	15

Erythrocytes normochromic microcytic with anisocytosis polychromatophilia poikilocytosis basophilic stippling and numerous normoblasts









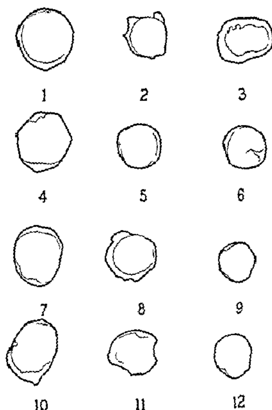





PLATE 28

ACUTE MYELOID LEUKEMIA

(MICROMYELOBLASTIC TYPE)



Cells 1 4 7 and 10 are myeloblasts of intermediate size They show variable nucleolar structures ranging from one to three in number with only a slight fringe of cytoplasm Cells 2 5 8 and 11 are micromyeloblasts showing a slight cytoplasmic fringe with nucleoli from one to three in number Cells 3 6 9 and 12 are atypical small myeloblasts sometimes confused with small lymphocytes

of thromboplastin rarely exists Deficiency of blood platelets causing thrombocytopenic purpura is by far the most common cause of hemorrhages and purpura Then there may be quantitative or qualitative alterations in the effectiveness of the various agents concerned in coagulation such as are believed to exist in hemophilia

In the evaluation of a purpuric *problem it is important that certain* laboratory procedures be followed in order to classify properly the exact deficiency responsible for the purpuric state All hemorrhagic states should be divided into three large groups as follows

1 Those caused by decreased numbers of platelets
2 Those caused by a failure of the clot to form
3 Those caused by weakness of the capillaries

The hemorrhagic states characterized by diminished numbers of platelets include such conditions as splenic thrombocytopenic purpura where platelets are apparently being destroyed in excessive numbers aplastic anemia where platelets are not produced in adequate number in the bone marrow leukemia of various types septicemias arsenic, benzene and radium poisoning affecting bone marrow output megakaryocytic aplasia in the marrow and the action of drugs on the marrow such as the thrombocytopenia produced by the analgesic agent sedormid and in *some instances by the sulfonamide* drugs

When a deficiency of platelets exists, the purpura is then said to be thrombocytopenic A careful history should exclude all possibilities with regard to drug ingestion and exposure to chemical agents Other conditions that might be responsible for thrombocytopenia are usually excluded in a routine blood examination Bone marrow studies are important in indicating any impairment of function in the production of platelets In all cases of purpura cer*tain laboratory procedures should be* carried out including the following

Red-cell count
White-cell count
Hemoglobin estimation
Differential cell count
Platelet count
Clot retraction time
Prothrombin estimation
Coagulation time
Bleeding time
Tourniquet test —in some instances
Fibrinogen determination—in rare cases

Only after this information is assembled is it possible to determine whether the purpura is thrombocytopenic, whether it is caused by prolonged coagulation whether it is on the basis of prothrombin deficiency or whether it is caused by weakness of the capillaries If the purpura is on the basis of prolonged coagulation of the blood with a normal platelet count the exact nature of the defect will most likely be revealed in the results of the above studies In this way the hemorrhagic disorder can be classified accurately and treat*ment directed intelligently toward* the existing deficiency In those cases in which no abnormality in the clotting factors or in the blood platelets

15

The Hemorrhagic Diseases

The substances necessary for proper coagulation of blood and cessation of hemorrhage are the following

1 *Fibrinogen* is formed in the liver and is found in the blood in concentration of 4/10 of 1 per cent It is the precursor of fibrin strands
2 *Prothrombin* the inactive precursor of thrombin is also formed in the liver The precursor of prothrombin is vitamin K which must be taken in the ordinary diet in sufficient amount to maintain normal prothrombin levels
3 *Antithrombin* or heparin is also formed in the liver and is released in amounts sufficient to prevent the activation of prothrombin under normal conditions
4 *Calcium salts* are present in whole blood to the extent of about 10 mg per 100 cc
5 *Thromboplastin* or cephalin (thrombokinase) is not present in blood plasma but is derived from tissue juices and to some extent from blood platelets This substance initiates the clotting process
6 *Blood platelets* or thrombocytes are present in normal blood to the extent of about 300 000 per cu mm and play their most important role in causing the clot to retract giving strength and firmness to the clot

Normal coagulation of blood takes place through a mechanism of interaction of these substances as follows

Thromboplastin plus antithrombin = the release of prothrombin

Prothrombin plus calcium = formation of thrombin

Thrombin plus fibrinogen = formation of fibrin strands

Fibrin strands plus the cellular elements of the blood = the completed clot

Hemorrhage does not stop at this point since the completed clot must then be acted upon by platelets and its retraction produced and this results in cessation of hemorrhage

Based upon the above considerations a deficiency of fibrinogen could exist in far advanced diseases of the liver such as atrophic cirrhosis and Banti s disease Contrary to older belief deficiency of calcium is not important in prolongation of the coagulation time Deficiency of prothrombin or its precursor vitamin K exists in inadequate dietary intake of this vitamin the absence of bile in the intestinal tract (since bile is required as the agent by which the vitamin is transported through the intestinal barrier) impaired absorptive intestinal surface and impairment of liver function to the extent that it is unable to convert the vitamin into prothrombin A deficiency

16

Infectious Mononucleosis

(See Plate 29 pp 122 125)

This disease which is sometimes called benign lymphadenosis or glandular fever is characterized by a relatively sudden onset out of full health—usually a sore throat generalized lymphadenopathy a febrile course and a fairly characteristic type of blood picture with ultimate recovery in nearly all cases The etiology is entirely unknown but evidence indicates that it is a virus disease transmitted probably from person to person It is seen usually in children and in young adults although no age is immune It occurs in both sporadic and mild epidemic forms and the onset may be sudden or gradual

Patients usually complain of fatigue headache and general malaise followed by low grade fever sore throat and variable degrees of lymphadenopathy In severe cases there may be joint pains chills and sweating In nearly all patients the cervical the axillary and the inguinal glands are enlarged Some may show only sore throat headache and malaise[1] with no lymphadenopathy others will present generalized lymphadenopathy as the chief and perhaps the only complaint still others will show gastro-intestinal symptoms mainly and a few will show symptoms that are referable to signs of meningeal irritation The spleen is enlarged in about 50 per cent of the cases A considerable number show an outbreak of body rash very similar to that seen in German measles

HEMATOLOGIC FINDINGS

In nearly every patient the diagnosis can be made by the characteristic blood picture The red cells the hemoglobin and the thrombocytes are usually unaffected The total white-cell *count is neither constant* nor typical in this disease Many of the patients develop a leukopenia usually in the early stage of the disease at which time the total *number* of cells may be only 3000 or 4000 per cu mm However later in the illness there is usually a definite leukocytosis with the cell increase being caused by the presence of a high percentage of atypical lymphocytic cells The average leukocyte count in infectious mononucleosis is probably 15 000 cells per cu mm

The *differential count* is the striking feature of the blood picture The various types of cells that may be seen in this disease are shown in Plate 29 The cells appear to be lymphocytic in character they vary considerably in size and in shape the nuclei show very irregular pat

is found, the purpuric state can be presumed to exist on the basis of capillary weakness This is frequently allergic in nature because of focal infection nutritional vitamin C deficiencies susceptibility to ingestion of drugs and infections of various types giving rise to various purpuric disorders such as Henoch s syndrome and Schonlein s purpura If no cause can be determined for the thrombocytopenia then splenectomy is the treatment of choice When the purpura is characterized by prolonged coagulation a family history usually establishes a diagnosis of hemophilia for which no specific treatment is effective except blood transfusions or supportive measures If the prothrombin is inadequate the deficiency can be adequately treated by the use of vitamin K

PLATE 29









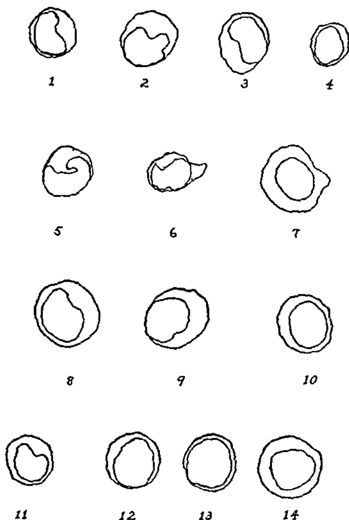












Figs 1-6 Pathologic leukocytoid mature lymphocytes from case of Type 1 Clinical picture of this patient was almost similar to that of acute leukemia but blood contained no immature cells

Fig 7 Characteristic cell of Type 2 Nuclei of these cells frequently resemble those of plasma cells derived from lymphocytes Cytoplasm is not so basophilic and not so vacuolated as in Type 1

Figs 8-11 Cells from Type 3 In general cells resemble those of Type 1 but some of them show leukemic features such as azurophil rod in the large vacuole of Figure 2 narrow bodied cells with indented nuclei (not illustrated) and cells with nuclei which are more or less immature i e with diffuse sievelike arrangement of chromatin and nucleoli (Figs 8 and 9)

Figs 12-14 Immature cells from case of acute lymphatic leukemia These are included to facilitate comparison of infectious mononucleosis with acute lymphatic leukemia Total count and lymphocyte percentage in this case were similar to counts in Case 1 (Figs 1-6) After Downey and McKinlay

(Downey Hal ed Handbook of Hematology New York Hoeber)

17

The Bone Marrow

(See Plate 30 pp 126 127)

In recent years examination of the bone marrow has assumed considerable importance as an aid in the more difficult diagnostic problems of hematology It is not necessary that the bone marrow be examined in all blood dyscrasias since a diagnosis can usually be established by examination of peripheral blood alone when taken in conjunction with the history and the clinical findings In rare instances however examination of the marrow provides additional or confirmatory information of great value in establishing an accurate diagnosis

The bone marrow is responsible for the production of three of the major cell types of blood that is the granulocytes the erythrocytes and the thrombocytes These cells and all their precursors therefore can be seen in the bone marrow Thus the marrow is an excellent tissue for study of the various undifferentiated cells including myeloblasts, premyelocytes myelocytes, promegaloblasts megaloblasts megakaryocytes reticulum cells endothelial cells etc The distribution and the relative percentages of these cells are of some importance in evaluating the bone marrow picture A differential count for normal marrow is shown in the following table

THE DIFFERENTIAL COUNT

Cell types to be listed in performing a differential count of bone marrow are as follows (figures indicate normal range in per cent)

Undifferentiated cells	0 0
Myeloblasts	0 0 1.2
Premyelocytes	
Neutrophil	0.5 9 0
Eosinophil	0 1 2 0
Basophil*	0 0
Myelocytes	
Neutrophil	10 0 34 6
Eosinophil	0.3 2 0
Basophil	0 0- 0.3
Metamyelocytes	
Neutrophil†	14 8 33 0
Eosinophil	0.3 3 7
Basophil	0 0- 0.3
Segmented forms	
Neutrophil	3 0 17 4
Eosinophil	0 1 1 0
Basophil	0 0- 1 0
Promegaloblasts	0 0
Megaloblast	0 0
Erythroblasts	4.2 18.2
Normoblasts	13.3 ?0 0
Megakaryoblasts	0 0 0 25
Megakaryocytes	0 25 0 9
Reticulum cells	0.2 2 0
Endothelial cells	0 1 0 6
Lymphocytes	0 0- 1 8
Plasmocytes	0 0 1 0

* B sophil are not encountered in paraff sec

† Metam locytes includ both ; n l and tab f rm of the S h l ng cl ss fication

terns some being round and some showing nuclear projections the cytoplasm in many cells is rather dark blue particularly at the periphery but in many instances it shows a rather marked clear perinuclear zone Furthermore vacuolization of the cytoplasm is a fairly constant feature in some cells The leukocytes may be so atypical that frequently they are confused with blast cells that may be seen in cases of leukemia and indeed many cases of infectious mononucleosis have been thought to be leukemia during the height of the cellular changes In nearly every case it is possible to make the diagnosis with fair certainty on the basis of the blood picture particularly if the white cell count is high In the leukopenic cases however there is usually more difficulty in diagnosis

THE HETEROPHIL ANTIBODY TEST

Diagnosis in all cases can be made with practical certainty by the use of the heterophil antibody test This consists in preparing serial dilutions of the patient s serum and into these are placed standard quantities of normal sheep cells approximately four days old The blood serum of the patient with infectious mononucleosis will show strong agglutination titers against these sheep cells In some cases the test may not be positive in the early stages of the disease but it may become so later during the course of the illness A positive heterophil antibody test of 1 64 or above indicates that the disease is infectious mononucleosis

Approximately 20 per cent of the patients with this disease will show a positive serologic test that is a positive Kahn or Wassermann reaction This positive test as well as the heterophil antibody test disappears within a few weeks after termination of the illness One should use extreme care to avoid labeling such a patient as syphilitic The prognosis of infectious mononucleosis is very good Fatalities are so infrequent that they are never expected There is no specific treatment for the disease and symptomatic treatment is all that is necessary Full recovery usually takes place in from two to three weeks

17

The Bone Marrow

(See Plate 30 pp 126 127)

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THE DIFFERENTIAL COUNT

Cell types to be listed in performing a differential count of bone marrow are as follows (figures indicate normal range in per cent)

Undifferentiated cells	0 0
Myeloblasts	0 0 1.2
Premyelocytes	
Neutrophil	0 5 9 0
Eosinophil	0 1 2 0
Pa ophil*	0 0
Myelocytes	
Neutrophil	10 0-34 6
Eosinophil	0.3 2 0
Basophil*	0 0- 0.3
Metamyelocytes	
Neutrophil†	14 8-33 0
Eosinophil	0.3 3 7
Basophil	0 0- 0.3
Segmented forms	
Neutrophil	3 0 17 4
Eosinophil	0 1 1 0
Basophil*	0 0 1 0
Promegaloblasts	0 0
Megaloblast	0 0
Erythroblasts	4 18 2
Normoblasts	13.3 20 0
Megakaryoblasts	0 0 0 25
Megakaryocytes	0 25 0.8
Reticulum cells	0 2 2 0
Endothelial cells	0 1 0 6
Lymphocytes	0 0- 1 8
Plasmocytes	0 0 1 0

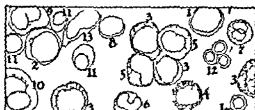
* Basophil ar n t cou t ed in pa affin sect

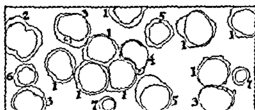
† Met m l cytes in l d both l d tab f rms f th Sch ll l h tio

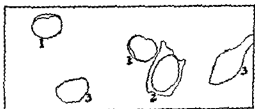
PLATE 30

BONE MARROW*

(NORMAL HYPERPLASTIC APLASTIC)





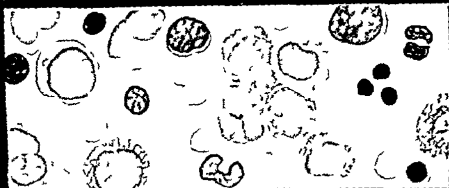


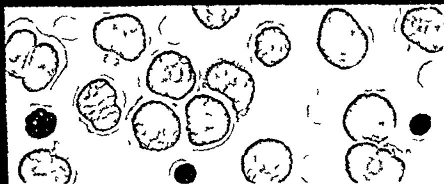
Top Normal Bone Marrow
1 Myeloblast
2 Premyelocyte
3 Neutrophilic myelocytes
4 Eosinophilic myelocyte
5 Juvenile neutrophils
6 Band neutrophil
7 Segmented neutrophil
8 Lymphocyte
9 Monocyte
10 Megakaryocyte
11 Macroblasts
12 Normoblasts
13 Primitive free cell (?)

Center Hyperplastic Bone Marrow with Maturation Arrest at Myeloblastic Level (from Patient with Acute Myeloblastic Leukemia)
1 Myeloblasts
2 Myeloblast in division
3 Premyelocytes
4 Myelocyte
5 Megaloblasts
6 Macroblast
7 Normoblasts

Bottom Aplastic Bone Marrow (from Patient with Aplastic Anemia)
1 Lymphocytes
2 Primitive free cell (?)
3 Degenerating cells

* *Drawn from serum spread*







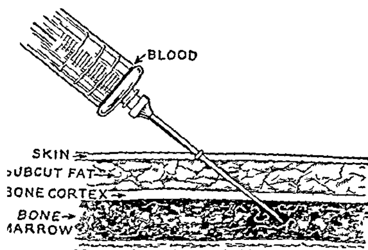


FIG 1 Showing position for injection of large bore needle with stylet (15 gauge average) The needle is thrust through the locally anesthetized skin and fascia then through the ventral plate of the sternum into the myeloid cavity

Under normal conditions there is great variation in the relative percentages of the immature cell types encountered in the marrow This is because one can never be sure as to exactly what type of specimen is removed through the aspirating needle Furthermore certain parts of the marrow may be relatively acellular while others are comparatively cellular Also the point of the aspirating needle in many instances does not dislodge adequate pieces of marrow tissue so that the real cytologic pattern can be studied Quantitative studies of marrow cells therefore have little value It is only when there are significant qualitative alterations in the marrow cellular picture that the findings have true and reasonable significance

In general bone marrow may be removed by one of two methods First and most popular is the aspiration of marrow from the sinusoidal spaces of the sternum A large bore needle with a stylet (average 15 gauge) is thrust through the anesthetized skin and fascia then through the ventral plate of the sternum into the myeloid cavity The stylet is withdrawn a syringe is attached and bone marrow mixed with blood is withdrawn Smears are prepared at once by expressing a small amount of blood on glass slides and smearing as with peripheral blood The material can be squirted into a watch crystal small flecks of marrow tissue removed with a pair of forceps and imprint preparations made on the surface of a glass slide Aspirated

marrow should not be mixed with any type of anticoagulant since this distorts the cellular picture to a considerable extent and renders the material considerably less valuable Examination of material removed in this way has very definite limitations and a method of greater value is the trephine method of removal of a button of bone and attached marrow so that preparations can be studied by the usual methods of histologic sectioning and staining with hematoxylin and eosin Only in this way is it possible to obtain a specimen adequate for histologic examination However this is a major-operating room procedure and for this reason it has not come into wide popularity

Plate 30 shows three types of bone marrow as follows The upper third of the plate represents marrow that can be considered to be normal because of the distribution of the various types of immature cells while the mid portion shows a type of marrow that is usually encountered in cases of acute myeloblastic leukemia and also in some cases of agranulocytosis—that is arrest of maturation of myeloblasts at the myeloblastic level The lower third of the plate shows the type of pattern that may be seen in a typical case of aplastic anemia which is a gross diminution in the number of cells with practically complete absence of the precursors of granulocytes erythrocytes and thrombocytes

In general the type of pathologic change found in bone marrow can be expressed only in a rather broad and general way In a study of the marrow one may find changes that can best be described under the following headings

1 *Normal marrow* with a type of cell distribution that includes all types of immature normal cells of the granulocytic the erythrocytic and the thrombocytic series including megaloblasts megakaryoblasts and various myeloblasts and all cells between those stages and the adult forms Normally the erythroid myeloid ratio varies from one to two to one to six in healthy adults These cells together comprise from about 90 to 95 per cent of the total cells

2. *The Erythroblastic Marrow* This is seen in any type of anemia in which there is an adequate bone marrow response It merely indicates that the bone marrow is quite active and capable of responding in a normal fashion It is found in various types of hemolytic anemias after acute and chronic blood loss and in treated cases of iron-deficiency anemia The marrow is characterized by predominance of the erythroblastic elements of all types

3 *Megaloblastic Marrow* This type of marrow is one in which megaloblasts predominate almost to the exclusion of normoblasts This type is seen most often in pernicious anemia and in other types of macrocytic anemia as those of sprue pregnancy fish tapeworm infestation pellagra and achrestic anemia Administration of specific antianemia factor usually causes the megaloblastic pattern to be

come normoblastic within a few days

4 *Leukemic Marrow* The marrow in chronic myelogenous leukemia shows merely an increase in the granulopoietic elements with the orderly maturation of cell types very little disturbed About the same type of cellular pattern as is seen in the peripheral blood can be observed in the marrow In the acute leukemias the marrow usually is crowded with myeloblasts regardless of whether the leukemia is in an aleukemic phase or in a phase of high peripheral cell count

5 *Other Conditions* In Gaucher s disease the outstanding finding is the presence of large fat laden typical Gaucher cells associated with a marrow pattern that appears to be normal or hyperplastic In myelomatosis the marrow may show considerable numbers of the typical plasma cells characteristic of that disease In kala azar there may be found an occasional large endothelial cell that contains typical Leishman Donovan bodies Infectious mononucleosis will show considerable numbers of the atypical lymphocytes characteristic of that disease The marrow in agranulocytosis usually shows maturation arrest at the myeloblastic level similar to the picture seen in acute leukemias The marrow in sickle cell anemia Cooley s anemia von Jaksch s anemia familial hemolytic icterus erythroblastosis foetalis and other types of hemolytic anemia is characterized by erythrocytic hyperplasia The marrow in polycythemia vera is not characteristic The marrow in aplastic anemia shows a simple decrease in the number of mature and immature forms of the three types of cell series The marrow findings in the various types of purpura are not very helpful In some cases of thrombocytopenic purpura the megakaryocytes appear to be quite normal and are present in normal numbers

It should be emphasized that bone marrow studies should be made only by an experienced hematologist one who is capable not only of interpreting cell types but of interpreting the findings and applying them in their proper relationship to the peripheral blood findings and the clinical findings Bone marrow findings are simply an adjunct to information derived from study of the patient as a whole An absolute diagnosis can not be made from the study of the bone marrow except in the most rare and isolated instances

18

Blood Parasites

(See Plates 31 and 32 pp 132, 133 136 137)

MALARIAL PARASITES

Plate 31 shows the various types of malarial parasites with the bottom row of cells showing blood platelets in order that they may be compared in morphology with the ring forms of the parasite Untrained workers may at times make the serious mistake of interpreting blood platelets lying on top of red cells as being malarial parasites

Plasmodium Vivax

This parasite which causes tertian malaria requires 48 hours to undergo complete schizogony It is seen first in ring forms the rings having a diameter of about three micra With polychrome dyes the nucleus of the ring stains red and the cytoplasm a bluish color As the parasite enlarges it assumes many shapes within the red cell After six hours most of the rings have become ameboid in shape and contain a slight amount of pigment The parasitized erythrocyte is larger swollen and paler and may show granular dots After 36 hours the parasite begins to divide into two four eight and finally a number of nuclei ranging from 12 to 24 By this time the erythrocyte is quite large Each of the nuclei is then known as a merozoite and the red cell is about ready to rupture Rupture takes place which is accompanied by a chill.

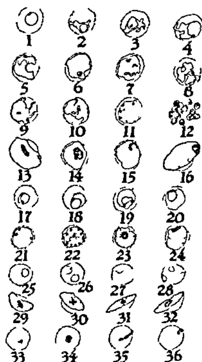
Plasmodium Malariae

The cycle of this parasite which causes quartan malaria requires 72 hours for completion and its development is similar to that of Plasmodium vivax The ring forms are approximately the same size but the cytoplasm is denser However it is extremely difficult to distinguish between Plasmodium vivax and Plasmodium malariae One outstanding characteristic of this parasite during the stage of growth is to stretch across the erythrocyte in the form of a band The infected red cells appear to shrink rather than enlarge The nucleus of this parasite divides to form eight or ten daughter nuclei arranged round centrally located pigment When fully matured the merozoites make a rosette form completely filling the erythrocyte.

Plasmodium Falciparum

This type of parasite which causes estivo-autumnal malaria does no have the regularity of schizogony of the two preceding ones, but apparently it occurs in variable periods from 36 to 48 hours The ring forms

MALARIA PARASITES
(Blood Platelets on Bottom Row)

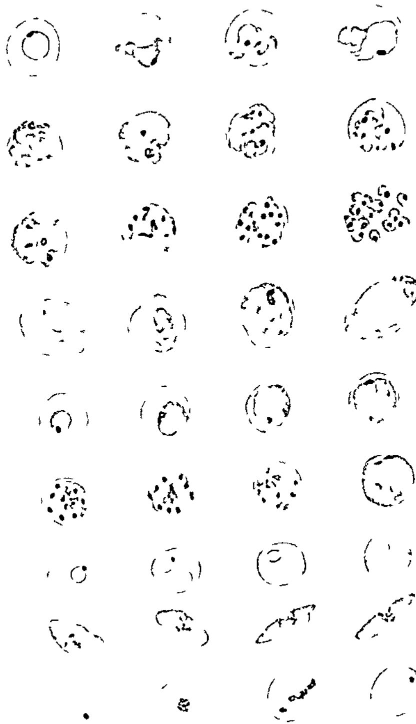


Plasmodium Vivax (Tertian)
1 Ring form
2 Ameboid form and Schuffner s dots in the erythrocyte
3 4 and 5 Ameboid forms
6 7 and 8 Schizonts
9 10 and 11 Segmenting stages
12 Liberated merozoites
13 and 14 Microgametocytes
15 and 16 Macrogametocytes

Plasmodium Malariae (Quartan)
17 Ring form
18 19 and 20 Schizonts
21 and 22 Segmenting stages
23 Microgametocyte
24 Macrogametocyte

Plasmodium Falciparum (Estivo Autumnal)
25 Ring form
26 Double infection of erythrocyte
27 Ring form with two chromatin dots
28 Triple infection of erythrocyte
29 and 30 Microgametocytes (crescent)
31 and 32 Macrogametocytes (crescent)

Blood Platelets
33 34 35 and 36 Blood platelets superimposed upon erythrocytes Shown in this plate because they are frequently confused with malaria parasites by the untrained laboratory worker



are much smaller and multiple infections in a single red cell are quite common The nucleus often shows two red chromatin dots rather than a single one Usually the blood shows only ring forms within the parasitized red cells and the crescent shaped gametocytes The presence of the crescent shaped gametocytes or the so called estivo autumnal crescents *is the single finding that indicates* most strongly that the parasite is of the falciparum type The adult schizont is much smaller than the erythrocyte The merozoites vary in number from 8 to 24 For details of the clinical symptoms physical findings and treatment of malaria the student should consult works in which these subjects are treated more extensively

RAT BITE FEVER (See Plate 32)

The cause of rat bite fever is the Spirillum minus It usually measures from three to six micra in length *and two tenths micron in thickness* It can be demonstrated in fresh blood by darkfield illumination where the organism is seen as a rapidly motile organism The best method of diagnosis is to inject the patient s blood intraperitoneally into white mice and the organisms then demonstrated in the tail blood about four or five days after inoculation

RELAPSING FEVER

(See Plate 32)

The cause of this disease is the Spirochaeta recurrentis The organisms are from 20 to 30 micra in length and twenty five hundredths micron in thickness The spirals are quite coarse and the organisms usually move in either direction with a spiral rotation They are more easily demonstrated by darkfield illumination in a drop of fresh blood under a cover slip They usually occur in the blood in the early stage of the disease, particularly during febrile periods

TRYPANOSOMIASIS

(See Plate 32)

The three species of trypanosomes are responsible for the disease trypanosomiasis — the Trypanosoma *gambiense for it in West Africa* the *Trypanosoma rhodesiense in* East Africa and the Trypanosoma cruzi in South America All may be found at times in the peripheral blood in aspirated lymph node material and in spinal fluid They are most often found early in the disease and demonstrated best by darkfield examination of fresh blood under a cover slip As in all other blood parasites *the best chance of demonstrating* these organisms is by thick film methods

LEISHMANIASIS

(See Plate 32)

The two clinical types of leishmaniasis the cutaneous type (tropical sore) and the visceral or systemic type (kala azar) are caused by Leishmania tropica and Leishmania donovani respectively They invade phagocytic cells primarily but if such cells burst then they escape into the blood stream The Leishman Donovan bodies are rarely found in ordinary thin blood films but more readily in thick film preparations Cen

trifugation of blood will usually throw the heavier parasitized cells to the bottom of the tube where they can be removed and thick films prepared Leishman Donovan bodies are oval from two to five micra in length The organisms can be demonstrated best by material from splenic puncture rather than from examination of blood

FILARIASIS (See Plate 32)

Filariasis is usually caused by the organism Wuchereria bancrofti in which the microfilariae may be found in the peripheral blood under ordinary fresh blood cover slip preparations They are quite actively motile and since they are quite large they thrash about causing great disturbance amongst the blood cells Therefore they can be searched for using the low power objective They are found more often in peripheral blood at night and the patients should be examined at that time

LEPTOSPIROSIS*

This disease is caused by the Leptospira icterohaemorrhagiae It is sometimes called Weil s disease The organism is a spirochete of from 7 to 14 micra in length and twenty five hundredths micron in thickness The spirals are small measuring only five tenths micron from crest to crest. They are best demonstrated in fresh blood by darkfield illumination They may be found in the blood up to the tenth day but in the urine as long as up to the hundredth day They can be demonstrated best by injecting blood or urine into guinea pigs On suspicion of this disease agglutination tests can be done if blood is sent to the National Institute of Health Washington D C

HISTOPLASMOSIS (See Plate 32)

This disease is caused by the Histoplasma capsulatum which is a fungus belonging to the Cryptococcus group The organism as found in man closely resembles the Leishman Donovan body It is oval about three micra in size When seen in the blood it shows a refractile cell membrane under which is a clear zone and then a small crescent blue mass surrounding a small vacuole It is usually found in phagocytic cells in the blood but can be seen in monocytes and can sometimes be found in marrow cells when apparently absent in the blood The disease is characterized by intermittent fever enlarged liver and spleen and leukopenia

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PLATE 32

Blood parasites Photomicrographs of specimens stained with Giemsa s stain

Figs 1 and 2 *Spirillum minus organism of rat bite fever* $\times 2000$

Fig 3 Spirochaeta recurrentis organism of relapsing fever $\times 1500$

Fig 4 Histoplasma capsulatum in a large mononuclear leukocyte in peripheral blood Vanderbilt University Hospital case Note thick capsule crescentic nuclear chromatin and vacuole There is *no* parabasal rod as in Leishmania Giemsa stain $\times 1500$

Fig 5 Trypanosoma rhodesiense organism of East African trypanosomiasis $\times 1500$

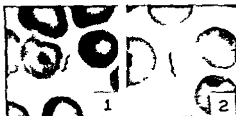
Fig 6 Trypanosoma cruzi organism of American trypanosomiasis $\times 1500$

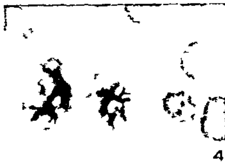
Fig 7 Trypanosoma lewisi organism of rat trypanosomiasis $\times 1500$

Fig 8 Leishmania tropica Leishman Donovan bodies in large mononuclear phagocyte from oriental boil $\times 1500$ Morphologically similar to Leishmania donovani of kala azar

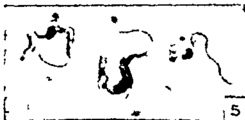
Fig 9 Larva of Wuchereria bancrofti in peripheral blood $\times 500$ Note sheath stained red with Giemsa s stain

Adapted from Kracke and Parker Textbook of Clinical Pathology Baltimore Williams & Wilkins

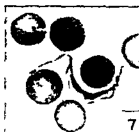

1
2


4


3


5


6


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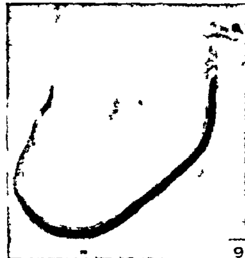

9

PLATE 32

Blood parasites Photomicrographs of specimens stained with Giemsa s stain

Figs 1 and 2 *Spirillum minus* organism of rat bite fever ×2000

Fig 3 *Spirochaeta recurrentis* organism of relapsing fever ×1500

Fig 4 *Histoplasma capsulatum* in a large mononuclear leukocyte in peripheral blood Vanderbilt University Hospital case Note thick capsule crescentic nuclear chromatin and vacuole There is no parabasal rod as in *Leishmania* Giemsa stain ×1500

Fig 5 *Trypanosoma rhodesiense* organism of East African trypanosomiasis ×1500

Fig 6 *Trypanosoma cruzi* organism of American trypanosomiasis ×1500

Fig 7 *Trypanosoma lewisi* organism of rat trypanosomiasis ×1500

Fig 8 *Leishmania tropica* Leishman Donovan bodies in large mononuclear phagocyte from oriental boil ×1500 Morphologically similar to *Leishmania donovani* of kala azar

Fig 9 Larva of *Wuchereria bancrofti* in peripheral blood ×500 Note sheath stained red with Giemsa s stain

Adapted from Kracke and Parker Textbook of Clinical Pathology Baltimore Williams & Wilkins

upon the extent of the disease its chronicity or acuteness and the type of lymph gland structure involved It has to be differentiated from such conditions as lymphosarcoma reticulo-endotheliosis reticulum cell sarcoma and even infectious mononucleosis The diagnosis is best established by biopsy of one of the affected lymph glands

POLYCYTHEMIA VERA

This is a progressive and ultimately fatal disease of unknown cause It is characterized by excessive numbers of red blood cells marked splenomegaly increased blood volume and the symptoms resulting from these altered states It is a disease of middle and late life occurring in both men and women Russian Jewish people seem to be more susceptible to it than others It occurs more commonly in males The fundamental cause of the disease is probably lowered oxygen tension in the bone marrow over a long period of time due to partial obliteration of the lumina of the nutrient arteries to the marrow It is therefore a disease of the vascular system and could be called thrombo angiitis obliterans of the bone marrow

Symptoms

The onset is insidious and the symptoms develop slowly but progressively The usual first symptoms are weakness and fatigue accentuated *cyanosis of face lips and mucous* membranes headaches dizziness and various types of paresthesia Abdominal and gastric disturbances are common The patient may have hemorrhages in the gastro intestinal tract and peptic ulcer is commonly seen as a complication of the disease The spleen is enlarged in practically all cases When associated with high blood pressure the disease is usually called polycythemia hypertonica or Geisbock s disease The diagnostic triad is the cyanotic color splenomegaly and the excessive number of circulating red cells

Blood Findings

The red cells are usually increased above seven million per cubic millimeter and the hemoglobin is increased in proportion Viscosity of the blood is from five to eight times normal Grossly the blood is very dark sticky and even viscous The total blood volume is increased from 50 to 100 per cent above normal There is an associated leukocytosis which in some cases is quite severe and even leukemoid so that the process may simulate leukemia

Treatment

The most satisfactory treatment includes methods to reduce the number of red cells This can be done by destroying the cells through the administration of acetylphenylhydrazine or by removing them mechanically through the process of repeated venesection The latter plan of treatment is preferred More recently the use of radioactive phosphorus has met with *general success and apparently this* agent is capable of maintaining the disease in prolonged periods of remission

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Miscellaneous Diseases of the Blood and the Blood-Forming Organs

HODGKIN'S DISEASE

This is a systemic febrile disease It is characterized by painless lymph gland enlargement, with a specific histologic structure

The etiology of Hodgkin's disease is entirely unknown Some believe it to be caused by a virus others that it is an infective type of granuloma and still others that it is an atypical form of tuberculosis More recently it is suspected to be a form of brucellosis

The disease is characterized by a primary involvement of the reticulo-endothelial system in which the chief lesions occur in the lymph nodes the spleen the liver and the bone marrow All or only part of the lymphoid tissues may be involved The nodes are firm large usually discrete but finally become matted together Microscopically Hodgkin's disease is characterized by a pleomorphic cytologic picture in which characteristic mononuclear and multinuclear giant cells occur among lymphocytes plasma cells eosinophils proliferating endothelium and varying amounts of fibrous tissue These characteristic giant cells are known as Sternberg or Dorothy Reed cells The histologic picture depends upon the chronicity of the process

The blood has been extensively studied in Hodgkin's disease but no blood changes occur with sufficient consistency to be considered characteristic Practically all cases are characterized by progressive hypochromic anemia The total leukocyte count is usually elevated In some instances extremely high counts have been recorded but even leukopenia may exist The leukocytosis is usually neutrophilic In other patients there is a lymphocytic increase and in still others the monocytes are considerably increased Eosinophilia is occasionally observed and may be quite high in some patients

The disease is seen mainly in young to middle aged people but may occur at any age It is more common in males The spleen is enlarged in most instances, and in occasional cases the disease seems to be restricted to the spleen Skin manifestations are fairly common pruritus being the most common disorder Bone marrow lesions are frequently found They are destructive lesions and sometimes perforate the cortex There is frequently a mild elevated temperature and various degrees of cachexia The symptoms and the physical signs vary widely and depend

hematologic findings are those previously described When the condition is suspected the mother s blood and the fetal blood should be tested for the presence or absence of the Rh factor and the mother s blood should also be tested for the presence of anti Rh agglutinins (see page 165)

Treatment

If Rh agglutination is found to be the basis of the condition then treatment is usually directed toward giving the infant multiple transfusions and only of Rh negative blood The blood of the mother should never be used since it merely transfers more of the agglutinins to the infant and the blood of the father should not be used as he is always Rh positive Furthermore the mother should not be permitted to feed the child at the breast since breast milk also contains anti Rh agglutinins The prognosis is usually fairly good when proper treatment is promptly instituted Normal blood findings are usually not established until about the second or the third month since some time is required for the disappearance of anti Rh agglutinins from the infant s blood

Rh FACTOR IN REPEATED TRANSFUSIONS

Since 85 per cent of the white population have the Rh agglutinogen in their blood cells and 15 per cent do not have it it is important that the Rh negative patient be transfused only with Rh negative blood particularly if it appears likely that he is to receive more than one transfusion The transfusion of Rh positive cells into the Rh negative patient results in the formation of anti Rh agglutinins which tend to destroy the next transfusion of Rh positive cells giving rise to post transfusion reactions massive cellular destruction clinical jaundice and in general loss of the blood that is transfused into the patient For that matter it is recommended that all Rh negative female patients who receive transfusions for any cause should always be given Rh negative blood

In Rh negative pregnant women it is particularly important that only Rh negative blood be used for transfusions In order to be safe especially in those areas where Rh factor determinations are not done routinely it is important that every pregnant woman who requires a transfusion be transfused only from an Rh negative donor and a pool of Rh negative donors should be established in all communities so that a supply of such blood may be available

Potent Rh typing sera may be obtained from the Boston Blood Grouping Laboratory 300 Longwood Ave., Boston Mass Lederle Laboratories New York 20 N Y and the Certified Blood Donor Service 146-16 Hillside Ave., Jamaica 2, N Y

Prognosis

Polycythemia vera is incurable but the life expectancy in the average case is many years. The blood of polycythemic patients is suitable for use as donor's blood.

ERYTHROBLASTOSIS FOETALIS

This condition is better termed hemolytic anemia of the newborn, of which the clinical state erythroblastosis foetalis is only the extreme manifestation. This disease occurs late in fetal life, at the time of birth, or shortly after birth. It is characterized by excessive destruction of erythrocytes reflected in the peripheral blood by the presence of numerous erythroblasts, a high reticulocytosis and a severe anemia, with the clinical findings of edema, extreme pallor and variable degrees of jaundice. This clinical picture is sometimes called fetal hydrops, universal edema of the fetus, familial icterus gravis or congenital anemia of the newborn.

Role of Rh Factor

The cause of hemolytic anemia of the newborn was entirely unknown until 1941, when it was noted that these infants were born of Rh negative mothers and the infants were Rh positive. The mechanism as proposed by Levine and subsequently established is to the effect that the cells of the Rh positive fetus escape through placental defects into the Rh negative maternal circulation and anti Rh antibodies in high titer develop in turn in the mother's blood. These antibodies are then diffused through the placental circulation into the fetus and large numbers of the fetal Rh positive cells thus destroyed. This situation results, therefore, in prolonged and intensive destruction of the fetal cells by the anti Rh agglutinins and in severe hemolytic anemia of the infant.

Although 15 per cent of females are Rh negative, erythroblastosis occurs only once in from about three hundred to four hundred births, when actually in approximately 12 per cent of all pregnancies there is an Rh negative mother and an Rh positive fetus. Certain other conditions must be necessary for production of the disease, including injury to the placenta and the fact that in many cases the Rh agglutinins never reach sufficiently high titer to produce cell destruction. The condition occurs more frequently in later pregnancies than in first and second pregnancies, indicating that some build up of anti Rh agglutinins in the maternal blood may be necessary. Although 90 per cent of the cases of erythroblastosis can be explained on this basis, the remaining 10 per cent may be caused by newly discovered Rh factors and perhaps even maternal and fetal incompatibility of the agglutinogens A and B.

Symptoms

The symptoms of erythroblastosis foetalis are those of a very severe hemolytic anemia. The infant is profoundly anemic, with edema and sometimes generalized anasarca, and shows a deepening jaundice. The spleen and the liver are frequently enlarged and easily palpable and the

a slow and gradual compensation for this tissue loss occurs in the form of generalized lymphadenopathy within a few months after splenectomy The phagocytic function is taken over by other endothelial elements in the capillary endothelium the lymph glands and the liver sinusoids

The spleen is not essential to life as has been demonstrated by the re moval of hundreds of traumatized normal spleens Also congenital ab sence of the spleen is not an unusual finding in a normal individual Ap parently there are no immediate or remote ill effects from splenectomy Patients who have been splenecto mized can be regarded as normal peo ple in every respect The immediate effect of splenectomy on the blood is an increase of hemoglobin and red cells in the vascular system In cases of essential thrombocytopenic pur pura there is an immediate increase of blood platelets and oftentimes a marked thrombocytosis The white cells also show an immediate increase after splenectomy regardless of the reason for which it is performed

The spleen should be removed in all cases of congenital hemolytic ic terus where it appears that th organ is incompatible with the well being of the patient Some patients with this disease go through their entire lives without the necessity of splenic removal However when the spleen is removed there is practically always a clinical cure

The spleen should be removed in verified cases of essential thrombo-cytopenic purpura since the clinical result from this procedure seems to be far more satisfactory than the tem porizing measures sometimes em ployed to control the hemorrhages of that disease

The spleen also should be removed in a considerable number of cases of so called Banti s syndrome This syn drome which is characterized by splenomegaly various degrees of liver damage signs of portal obstruc tion manifested by abdominal su perficial collateral circulation eso phageal varices with hemorrhages and leukopenia is sufficient indica tion to consider seriously the question of splenectomy Frequently the deci sion to remove the spleen should be made at the operating table after the liver has been examined In any case if the removal of the spleen does not exert any curative influence it pro vides the patient with considerable relief from symptoms of the enlarged organ

Recent indications for splenectomy include the syndrome known as pri mary splenic neutropenia described by Doan and his associates in which it is assumed that the spleen has an excessive lytic action for neutrophils This syndrome is characterized by enlargement of the spleen marked neutropenia for which no other cause can be discovered and a bone mar row that must be demonstrated to be normal and capable of producing adequate numbers of granulocytes This syndrome is adequate reason for splenectomy

The condition recently described by Doan as panhematocytopenia is also apparently relieved by splenec tomy In this syndrome the spleen is enlarged the bone marrow func tions normally or is capable of nor

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Splenomegaly and Splenectomy

The spleen is enlarged in a number of conditions. Some are closely related to blood diseases and others are more related to various disease processes such as infections. Common causes of splenomegaly are typhoid fever, generalized septicemia, solitary abscess of the spleen, subacute bacterial endocarditis, splenic tuberculosis, congenital syphilis, malaria, histoplasmosis, schistosomiasis and echinococcus disease. The following causes of splenomegaly are more closely related to diseases of the blood forming tissues: Banti's syndrome, congenital hemolytic anemia, acute and chronic acquired hemolytic anemia—rarely pernicious anemia, the Mediterranean anemias, erythroblastosis foetalis, chronic myelogenous leukemia, chronic lymphatic leukemia, polycythemia vera, infectious mononucleosis, solitary neoplasms such as hemangioma, lymphosarcoma and follicular lymphoma, Hodgkin's disease, Gaucher's disease, Niemann-Pick disease, Schuller-Christian's disease, amyloidosis, primary splenic neutropenia, splenic panhematocytopenia, Felty's syndrome, hemosiderosis and essential thrombocytopenic purpura in some cases. When one is confronted with a problem of splenomegaly consideration therefore has to be given to the large number and the wide variety of disease processes which include infectious diseases, metabolic disorders, circulatory disturbances, neoplastic conditions and the various blood diseases.

SPLENECTOMY

Removal of the spleen is clearly indicated in a small number of blood diseases and in a few other conditions as well. The indications for removal of the spleen are as follows:

1. Ruptured spleen with serious hemorrhage
2. Primary tumors of the spleen such as hemangioma
3. Congenital hemolytic icterus
4. Essential thrombocytopenic purpura
5. Banti's syndrome
6. Primary splenic neutropenia
7. Splenic panhematocytopenia

The spleen is an organ that consists chiefly of phagocytic reticulo-endothelium and lymphoid tissue supported by a fibrous network. It contains large vascular channels that promote a very sluggish flow of blood enabling the process of phagocytosis to be carried out efficiently. It has been estimated that removal of a normal spleen removes about one third of the lymphoid and the endothelial tissue of the body. The effects of splenectomy therefore are only those of removal of this amount of tissue as

a slow and gradual compensation for this tissue loss occurs in the form of generalized lymphadenopathy within a few months after splenectomy The phagocytic function is taken over by other endothelial elements in the capillary endothelium the lymph glands and the liver sinusoids

The spleen is not essential to life as has been demonstrated by the removal of hundreds of traumatized normal spleens Also congenital absence of the spleen is not an unusual finding in a normal individual Apparently there are no immediate or remote ill effects from splenectomy Patients who have been splenectomized can be regarded as normal people in every respect The immediate effect of splenectomy on the blood is an increase of hemoglobin and red cells in the vascular system In cases of essential thrombocytopenic purpura there is an immediate increase of blood platelets and oftentimes a marked thrombocytosis The white cells also show an immediate increase after splenectomy regardless of the reason for which it is performed

The spleen should be removed in all cases of congenital hemolytic icterus where it appears that the organ is incompatible with the well being of the patient Some patients with this disease go through their entire lives without the necessity of splenic removal However when the spleen is removed there is practically always a clinical cure

The spleen should be removed in verified cases of essential thrombocytopenic purpura since the clinical result from this procedure seems to be far more satisfactory than the temporizing measures sometimes employed to control the hemorrhages of that disease

The spleen also should be removed in a considerable number of cases of so called Banti s syndrome This syndrome which is characterized by splenomegaly various degrees of liver damage signs of portal obstruction manifested by abdominal superficial collateral circulation esophageal varices with hemorrhages and leukopenia is sufficient indication to consider seriously the question of splenectomy Frequently the decision to remove the spleen should be made at the operating table after the liver has been examined In any case if the removal of the spleen does not exert any curative influence it provides the patient with considerable relief from symptoms of the enlarged organ

Recent indications for splenectomy include the syndrome known as primary splenic neutropenia described by Doan and his associates in which it is assumed that the spleen has an excessive lytic action for neutrophils This syndrome is characterized by enlargement of the spleen marked neutropenia for which no other cause can be discovered and a bone marrow that must be demonstrated to be normal and capable of producing adequate numbers of granulocytes This syndrome is adequate reason for splenectomy

The condition recently described by Doan as panhematocytopenia is also apparently relieved by splenectomy In this syndrome the spleen is enlarged the bone marrow functions normally or is capable of nor

mal function and two or more of the marrow cellular elements are seriously depleted in the blood It is a condition in which the overactive spleen destroys too many white cells red cells platelets or any combinations of these cells It therefore, is a combination of hemolytic anemia thrombocytopenic purpura and splenic neutropenia As in primary splenic neutropenia, before the spleen is removed in this syndrome it should be determined definitely by marrow studies that the cellular depletion is not on the basis of marrow hypoplasia

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Blood Pictures in Various Laboratory Animals

(See Plate 33 pp 146 147)

Plate 33 shows the blood pictures found in various laboratory animals and also the blood of the camel and the human These types of blood, excepting that of the camel represent the ones usually employed in the course of experimental work The following average figures are representative of the hematologic findings to be expected in the various types of animals indicated

THE RABBIT

Erythrocyte count Normal range from 4 500 000 to 7 000 000 average 5 670 000 The erythrocytes are similar to human red blood cells with considerable anisocytosis poikilocytosis and polychromatophilia but no nucleated cells

Hemoglobin Normal range from 60 to 90 per cent (Sahli) average 75 per cent (Sahli)

Leukocyte count Normal range from 4 000 to 13 000 average 7 900

Differential count

	Range (per cent)	*Average (per cent)*
Neutrophils	30 50	43 4
Lymphocytes	30-50	41 8
Monocytes	2 16	9 0
Eosinophils	0 5 5	2 0
Basophils	2 8	4 3

Platelets Normal range from 200 000 to 1 000 000 average 400 000

THE GUINEA PIG

Erythrocyte count Normal range from 4,500 000 to 6 800 000 average 5 750 000 In general the erythrocytes are similar to human red blood cells with considerable anisocytosis and polychromatophilia and no nucleation

Hemoglobin Normal range from 80 to 100 per cent (Sahli)

Leukocyte count Normal range from 6 000 to 20 000

Differential count

	Range (per cent)	*Average (per cent)*
Pseudoeosinophils (Neutrophils)	3 50	41 8
Lymphocytes	35 55	45 3
Monocytes	1 20	8 4
Eosinophils	2 15	4 8
Basophils	0 2	0 7

Platelets Average about 500 000 per cu mm

THE MOUSE

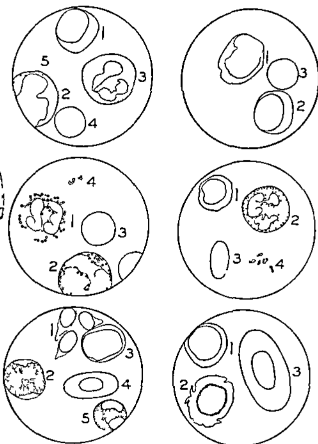
Erythrocyte count Normal range from 8 000 000 to 11 000 000 average 9 700 000 The erythrocytes are round biconcave disks generally nonnucleated with slight anisocytosis and marked polychromatophilia

Hemoglobin From 80 to 100 per cent (Sahli)

Leukocyte count 8 450

PLATE 33

BLOOD PICTURES IN VARIOUS LABORATORY ANIMALS



Upper left Normal human blood showing red cells as round biconcave disks nonnucleated average diameter 7.2 micra Cell 1 lymphocyte cell 2 a monocyte cell 3 a multilobed neutrophil cell 4 a normal red cell cell 5 a group of thrombocytes or blood platelets Monkey blood is identical

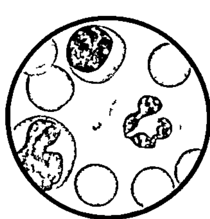
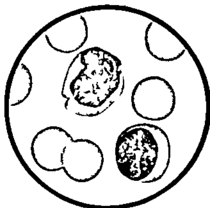
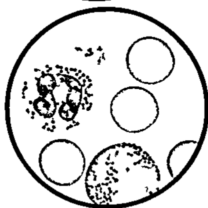
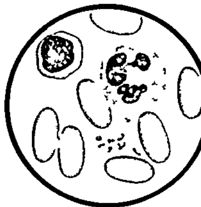
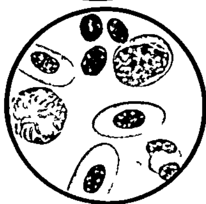
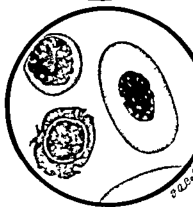
Upper right Blood of a large white rat, one of Wistar strain for laboratory purposes Red cells round biconcave disks as in human Average diameter 6.3 micra Neutrophils 2[illegible]% lymphocytes 65% White cells similar to human Similar blood picture seen in mice other rats guinea pigs cats dogs horses mules and pigs cows and oxen except for percentage variations in white cell Cell 1 large irregular lymphocyte cell 2 a small lymphocyte cell 3 a normal red cell No platelets shown since they are scarce

Center left Blood picture of a normal rabbit (New Zealand) used for laboratory purposes The red cells are round biconcave disks average diameter 6.7 micra and identical with human Rabbit does not have typical neutrophils but has 40% cells with multilobed nuclei and pseudo eosinophilic cytoplasm granules These are called amphophils as seen in cell 1 Cell 2 is a basophil cell 3 a normal red cell and cell 4 a group of platelets

Center right The blood of a camel drawn from actual smear Shown because the camel and members of the camel family are the only animals with oval nonnucleated red cell Average cell size 5 x 8 micra The sheep and the goat have normal round biconcave disks with a few oval nonnucleated cell Cell 1 a lymphocyte cell 2 an eosinophil cell 3 the normal red cell cell 4 a group of platelets similar to human

Lower left Blood of a chicken and similar to other fowl Most red cells are oval and nucleated Average size 7 x 12 micra A few round cells may be seen No typical neutrophils About 30% of white cells are multilobed with spindle shaped cytoplasmic containing bodies as in cell 2 Cell 1 a group of platelets cell 3 a lymphocyte cell 4 a normal red cell cell 5 an eosinophil

Lower right The blood of a frog Red cells oval and nucleated Average size 9 x 18 micra Neutrophil only [illegible]% Cell 1 a lymphocyte cell 2 probably a lymphocyte (40% were of this type) cell 3 the normal red cell

THE MOUSE (*Cont*)

Differential count

	Range (per cent)	Average (per cent)
Neutrophils	20 40	26.2
Lymphocytes	55 75	67 8
Monocytes	1 15	7.5
Eosinophils	1 5	2 0
Basophils	0 1	0.5

THE DOG

Erythrocyte count Normal range from 5 500 000 to 8 000 000 average 7,220 000 The red cells are round biconcave disks rather pale often appearing as ring forms There is considerable anisocytosis and nucleation

Hemoglobin From 90 to 100 per cent (Sahli)

Leukocyte count Normal range from 6 000 to 20 000 average 11 840

Differential count

	Range (per cent)	Average (per cent)
Neutrophils	60 75	69 0
Lymphocytes	10 30	20 0
Monocytes	2 12	6 1
Eosinophils	2 10	5 0
Basophils	0 2	0 7

Platelets Average about 350 000 per cu mm

THE MONKEY

Erythrocyte count Normal range from 5 000 000 to 7 000 000 average 5 590 000 The red cells are biconcave disks showing some variation in size with moderate polychromatophilia but no nucleation

Hemoglobin 90 per cent (Sahli)

Leukocyte count Normal range from 8 000 to 25 000 average 16 000

Differential count

	Range (per cent)	Average (per cent)
Neutrophils	30 50	42 2
Lymphocytes	40-60	52 8
Monocytes	1 12	1 5
Eosinophils	1 5	3 7
Basophils	0 1 0 5	0.3

Platelets Average about 25,000 per cu mm

THE RAT

Erythrocyte count Normal range from 7 000 000 to 10 000 000 average 8,500 000 The red cells are biconcave disks showing moderate anisocytosis marked polychromatophilia and an occasional nucleated cell

Differential count

	Range (per cent)	Average (per cent)
Neutrophils	15 40	27 0
Lymphocytes	50 80	67 9
Monocytes	2 7	5.3
Eosinophils	0 4	2 1
Basophils	0 1 5	0 7

Platelets Average from 600 000 to 700 000 per cu mm

THE CHICKEN

Erythrocyte count Normal range from 2 800 000 to 4 500 000 average 3 440 000 The red cells are oval and nucleated However there are a few round nucleated and nonnucleated forms

Hemoglobin 60 per cent (Sahli)

Leukocyte count Normal range from 20 000 to 40 000 average 25 000

Differential count

	Range (per cent)	Average (per cent)
Neutrophils	20 40	31 1
Lymphocytes	40 60	51 6
Monocytes	5 15	10 0
Eosinophils	2 10	5 9
Basophils	1 4	2 6

THE FROG

Erythrocyte count Normal range from 400 000 to 600 000 average 460 000 The red cell of the frog is oval and bi

convex with an oval nucleus Some of the cells are small with a small nucleus Nonnucleated forms may also be found

Hemoglobin 80 per cent (Sahli)

Leukocyte count Average 18,310

Differential count

	Average (per cent)
Neutrophils	7
Lymphocytes	59
Eosinophils	27
Basophils	7

NOTE All the figures given in this summary of the blood picture of laboratory animals have been taken from Scarborough's Monograph (Scarborough R A The Blood Picture of Normal Laboratory Animals New Haven Conn Yale 1927)

THE MOUSE (*Cont*)

Differential count

	Range (per cent)	*Average (per cent)*
Neutrophils	20 40	26 2
Lymphocytes	55 75	67 8
Monocytes	1 15	7 5
Eosinophils	1 5	2 0
Basophils	0 1	0 5

THE DOG

Erythrocyte count Normal range from 5 500 000 to 8 000 000 average 7 220 000 The red cells are round biconcave disks rather pale often appearing as ring forms There is considerable anisocytosis and nucleation

Hemoglobin From 90 to 100 per cent (Sahli)

Leukocyte count Normal range from 6 000 to 20 000 average 11 840

Differential count

	Range (per cent)	*Average (per cent)*
Neutrophils	60 75	69 0
Lymphocytes	10 30	20 0
Monocytes	2 12	6 1
Eosinophils	2 10	5 0
Basophils	0 2	0 7

Platelets Average about 350 000 per cu mm

THE MONKEY

Erythrocyte count Normal range from 5 000 000 to 7 000 000 average 5 590 000 The red cells are biconcave disks showing some variation in size with moderate polychromatophilia but no nucleation

Hemoglobin 90 per cent (Sahli)

Leukocyte count Normal range from 8 000 to 25 000 average 16 000

Differential count

	Range (per cent)	*Average (per cent)*
Neutrophils	30 50	47 2
Lymphocytes	40-60	52 8
Monocytes	1 12	1 5
Eosinophils	1 5	3 7
Basophils	0 1 0 5	0 3

Platelets Average about 25 000 per cu mm

THE RAT

Erythrocyte count Normal range from 7 000 000 to 10 000 000 average 8 500 000 The red cells are biconcave disks showing moderate anisocytosis marked polychromatophilia and an occasional nucleated cell

Differential count

	Range (per cent)	*Average (per cent)*
Neutrophils	15 40	27 0
Lymphocytes	50 80	67 9
Monocytes	2 7	5 3
Eosinophils	0 4	2 1
Basophils	0 1 5	0 7

Platelets Average from 600 000 to 700 000 per cu mm

THE CHICKEN

Erythrocyte count Normal range from 2 800 000 to 4 500 000 average 3 440 000 The red cells are oval and nucleated However there are a few round *nucleated and nonnucleated forms*

Hemoglobin 60 per cent (Sahli)

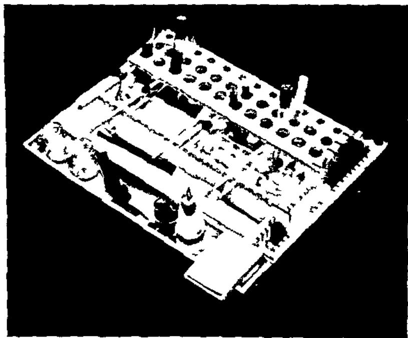
Leukocyte count Normal range from 20 000 to 40 000 average 25 000

Differential count

	Range (per cent)	*Average (per cent)*
Neutrophils	20 40	31 1
Lymphocytes	40 60	51 6
Monocytes	5 15	10 0
Eosinophils	2 10	5 9
Basophils	1 4	2 6

THE FROG

Erythrocyte count Normal range from 400 000 to 600 000 average 460 000 The red cell of the frog is oval and bi



A suitable tray for hematologic work constructed of light wood size approximately 12 x 14 inches Note bottles for alcohol diluting fluids and tourniquet in first compartment sterile wrapped syringes in second compartment dirty syringes and soiled cotton in third compartment Also note rack for holding pipettes sterile needles kept in cotton plugged tubes The holes are perforated in three different sizes Slide slots are at one end in which two slides are placed back to back clean cotton beneath small pad on corner

22

Hematologic Technic

Although there are many technics for the various hematologic procedures this section outlines only one for each test this being chosen on the basis of reliability ease of execution and accuracy The tests described herein are those used in the Hematology Laboratory at the Medical College of Alabama

It is better for the student or technician to become thoroughly skilled in the use of one test than to learn less about a larger number

METHODS OF OBTAINING BLOOD

Finger Puncture

Materials and Equipment

1 Instrument for puncture
   (A) Bard Parker knife blade size 11 with projected tip through a cork stopper
   (B) Hagedorn needle
   (C) Automatic blood lancet
   Needle making a round wound should not be used as it seals too quickly
2 Sponges gauze 2 in x 2 in or pledgets of cotton
3 Alcohol 70 per cent.

Procedure

1 Cleanse the end of the finger with 70 per-cent alcohol and allow to dry
2 Make puncture with a quick stroke deep enough to allow blood to flow freely Hard pressure will dilute the blood with tissue fluid
3 Wipe with a dry sponge
4 Press finger gently and the blood will form a round drop
5 Collect in order (1) Hemoglobin (2) Leukocyte count (3) Erythrocyte count (4) Smears for differential count
6 When collecting blood from an infant stick either the heel or the great toe Collect the specimens in reverse of steps listed above as the blood flows better a few seconds immediately after the puncture is made

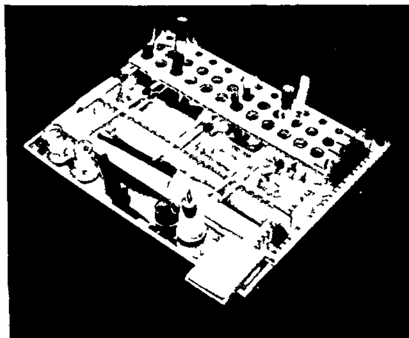
Venepuncture

Materials and Equipment

1 Sponges gauze or pledgets of cotton
2 Iodine tincture of
3 Alcohol 70 per cent
4 Tourniquet laboratory tubing 18 in long
5 Sterile dry syringe and needles from 19 to 22 gauge from 1 to 1½ in in length

Procedure

1 Apply iodine to the area Allow to dry Remove with alcohol
2 Place a tourniquet about 2 in above the site of puncture so that



A suitable tray for hematologic work constructed of light wood size approximately 12 x 14 inches Note bottles for alcohol diluting fluids and tourniquet in first compartment sterile wrapped syringes in second compartment dirty syringes and soiled cotton in third compartment Also note rack for holding pipettes sterile needles kept in cotton plugged tubes The holes are perforated in three different sizes Slide slots are at one end in which two slides are placed back to back clean cotton beneath small pad on corner

it may be released easily Do not constrict enough to cut off arterial circulation
3 Have the patient open and close fist a few times and then close fist tightly
4 Pull back on the plunger of the syringe to make sure that the needle is open Be sure that the needle is on tight then push the plunger back to its closed position
5 With the bevel up insert the needle under the skin and then into the vein
6 Withdraw quickly the amount of blood needed but do not hemolyze it by withdrawing it too fast
7 Release the tourniquet and then remove the needle When the needle is withdrawn apply pressure at the point of entry
8 Transfer the blood immediately to the proper containers
9 Rinse syringe and needle with cold water immediately

When obtaining blood from an adult the median cephalic or the median basilic vein in the bend of the elbow is usually used In very young children and infants it is sometimes necessary to draw blood from an external jugular vein or longitudinal sinus

ERYTHROCYTE COUNT

Materials and Equipment

1 Equipment for finger puncture
2 Water alcohol and ether for cleaning pipettes
3 Diluting fluid (see solutions)
4 Counting chamber (Bright line Spencer preferred)
5 Diluting pipettes certified
6 Microscope

Pipettes (clean by suction)

1 Run water through
2 Run alcohol through to remove water
3 Dry by running ether through and then allow air to evaporate the ether Pipettes must be dry

Counting chamber

1 Wash with water
2 Dry with clean soft cloth Do not scratch

Procedure

1 Clean the finger or the ear with alcohol 70 per cent
2 Puncture the clean area and wipe off first drop with a dry sponge
3 From a second drop draw the blood exactly to the 0.5 mark of the red pipette Remove the excess blood from the tip of the pipette
4 Draw the diluting fluid to the 101 mark without allowing the blood to run out Twirl the pipette slowly while filling it
5 Take pipette in hand between thumb and middle finger Shake sideways for 2 minutes
6 Place the cover slip in correct position over the ruled area of the counting chamber
7 Discard the first 3 or 4 drops leaving the pipette and as quickly as possible touch a drop to the edge of the platform of the counting chamber allowing it to flow under the cover slip but not into the moat round the ruled area of the counting chamber There must be no bubbles
8 Allow to settle for a few minutes

9 Examine under the microscope Lower the substage a little and focus with the 16-mm objective When the ruled area is found turn to the 4 mm objective to count

Calculation

1 The large central square (1 mm × 1 mm) (a primary square) of the counting chamber contains 25 secondary squares each of which contain 16 tertiary squares
2 Count all the red cells in 5 secondary squares including the cells which touch the top and the right hand line of each of the secondary squares counted Counts of these squares should not vary more than 15
3 Total these cells

Shorter Method To the total of the 5 squares add 4 zeros

Example Total in 5 squares is 421 To this add 4 zeros giving a red count of 4 210 000 per cu mm of blood

Explanation of Calculation

1 Depth of counting chamber = 1/10 mm
2 Primary square area = 1 × 1 mm (the large corner squares)
   Volume of primary square = 1/10 cu mm
   (1 × 1 × 1 10 = 1/10 cu mm)
3 Secondary square = 1/4 × 1/4 mm (large center square is ruled in 25 secondary squares)
   Volume of secondary square = 1/160 cu mm
   (1/4 × 1/4 × 1/10 = 1/160 cu mm)
4 Tertiary square = 1/20 × 1/20 mm
   (secondary square is ruled in 16 tertiary squares)
   Volume of secondary square = 1/4000 cu mm
   (1/20 × 1/20 × 1/10 = 1/4000 cu mm)
5 Since 5 secondary squares are counted this is 5 × 16 or 80 tertiary squares
6 If x = number of RBC counted in 80 tertiary squares then 1/80 of x or x/80 = number of RBC counted in 1 tertiary square
7 Cubic contents of a tertiary square is 1/4000 cu mm the number of RBC in 1 cu mm = 4000 × x/80
8 Since the blood is diluted 1 200 the calculation is therefore 4000 × x/80 × 200 = 10 000 which is the same as annexing 4 zeros In calculating odd dilutions substitute the dilution to be calculated in place of the 200 and work out the factor
9 Dilution of the pipette may be calculated by dividing the tenth mark to which the blood was drawn into 100 (Example If blood is drawn to the 1 0 mark and diluted to the 101 mark divide 1 into 100 The dilution is 1 100)

Normal red cells

Men	4 500 000-5 500 000
Women	4 000 000-5 000 000
Children	5 500 000-7 000 000

LEUKOCYTE COUNT

Materials and Equipment

The same as for erythrocyte count

it may be released easily Do not constrict enough to cut off arterial circulation

3 Have the patient open and close fist a few times and then close fist tightly
4 Pull back on the plunger of the syringe to make sure that the needle is open Be sure that the needle is on tight then push the plunger back to its closed position
5 With the bevel up, insert the needle under the skin and then into the vein
6 Withdraw quickly the amount of blood needed but do not hemolyze it by withdrawing it too fast
7 Release the tourniquet and then remove the needle When the needle is withdrawn apply pressure at the point of entry
8 Transfer the blood immediately to the proper containers
9 Rinse syringe and needle with cold water immediately

When obtaining blood from an adult the median cephalic or the median basilic vein in the bend of the elbow is usually used In very young children and infants it is sometimes necessary to draw blood from an external jugular vein or longitudinal sinus

ERYTHROCYTE COUNT

Materials and Equipment

1 Equipment for finger puncture
2 Water alcohol and ether for cleaning pipettes
3 *Diluting fluid (see solutions)*
4 Counting chamber (Bright line Spencer preferred)
5 Diluting pipettes certified
6 *Microscope*

Pipettes (clean by suction)

1 Run water through
2 *Run alcohol through to remove water*
3 Dry by running ether through and then allow air to evaporate the ether *Pipettes must be dry*

Counting chamber

1 Wash with water
2 Dry with clean soft cloth Do not scratch

Procedure

1 Clean the finger or the ear with alcohol 70 per cent
2 Puncture the clean area and wipe off first drop with a dry sponge
3 From a second drop draw the blood exactly to the 0 5 mark of the red pipette Remove the excess blood from the tip of the pipette
4 Draw the diluting fluid to the 101 mark without allowing the blood to run out Twirl the pipette slowly while filling it
5 Take pipette in hand between thumb and middle finger Shake sideways for 2 minutes
6 *Place the cover slip in correct position over the ruled area of the counting chamber*
7 Discard the first 3 or 4 drops leaving the pipette and as quickly as possible touch a drop to the edge of the platform of the counting chamber allowing it to flow under *the cover slip but not into the* moat round the ruled area of the counting chamber There must be no bubbles
8 Allow to settle for a few minutes

4 Then treat as new slides

Cover slips

1 Same as for new slides but do not flame

Procedure

Slide Method

1 Puncture finger as for count
2 Take a clean slide and gently touch it to the drop of blood Do not touch the finger
3 Place the slide between the third finger and the thumb of the left hand with the drop of blood on the top surface
4 Take a second slide and place the narrow edge of the slide in front of the drop of blood with the spreader slide angled toward the right hand at a 30 degree angle
5 Pull the spreader back until it comes in contact with the drop of blood Let the blood spread until it almost reaches the outer edges of the spreader slide
6 Then with a firm steady movement (not too rapid or too slow) smear the blood toward the opposite end of the slide in the left hand The thickness of the smear will depend upon (1) the angle of the spreader slide and (2) the rapidity of spreading movement The smaller the angle of inclination the thinner the smear
7 The quality of the smear will depend upon (1) the cleanliness of the slides (2) the use of a small drop of blood and (3) the angle of the spreader slide as well as the smoothness with which the spread is made
8 Air-dry

Cover slip Method

1 Puncture finger as for count
2 Take a clean cover slip and touch it to a very small drop of blood
3 Drop a clean cover slip on the one with the drop of blood on it so that the blood spreads fairly thin Let blood reach maximum spread
4 Then pull them apart in a plane parallel to the surfaces holding them by diagonal corners
5 Air-dry
6 Cover slips give a thinner and more even distribution of the leukocytes but they are harder to handle and are more likely to be spoiled by a beginner

Staining Method

1 Place slide on a rack with the blood side up A cover slip may be placed on a small cork stopper
2 Flood the surface with Wright's stain and allow to stand from 1 to 3 minutes depending on the stain
3 Flood with buffer (see solutions) until the slide is covered and a greenish metallic sheen appears on the top of the stain Allow to stand 3 or 4 minutes
4 Wash with distilled water Be sure to flood the stain from the preparation because pouring it off will cause a precipitate to be found on the smear Once there it cannot be washed off
5 Drain with the thin end of the preparation pointed upward
6 Air dry
7 Cover slips must be mounted on a slide when dry

Procedure

Same as for erythrocyte count except that leukocyte pipette is used. Draw blood to the 0.5 mark and dilute to the 11 mark.

Calculation

1. Count the number of leukocytes in the 4 primary squares using the 16 mm objective.
2. Total these cells.

Shorter Method: Multiply the total of the 4 squares by 50. The result is the number of leukocytes per cu mm of blood.

Explanation of Calculation

1. Cubic content of 4 primary squares is 4/10 cu mm.
2. If x equals the number of white cells counted in 4 primary squares, then the number in 1 cu mm = 10/4x.
3. White counts are usually diluted 1:20; therefore the count in undiluted blood would be 10/4x times 20 = 50x.
   (To calculate the dilution of a white pipette divide the number of tenths to which the blood was drawn into 10.)

Normal leukocytes

From 5 000 to 10 000 per cu mm of blood.

Correction of Leukocyte Count for Nucleated Red Cells

If a large number of nucleated red cells are present, the white count will have to be corrected for these cells as they resemble leukocytes in the counting chamber.

1. Examine the stained smear under oil immersion.
2. Count the number of nucleated red cells seen while doing a differential of 100 leukocytes.
3. Multiply the number of nucleated red cells by the white cell count in hundreds. Subtract this number from the original leukocyte count. The resulting figure is the corrected leukocyte count.

Example

Uncorrected white-cell count 25 000
Nucleated cells per 100 WBC 25
250 × 25 = 6250
25 000 − 6 250 = 18 750 actual leukocytes

DIFFERENTIAL CELL COUNT

Materials and Equipment

1. Equipment for finger puncture
2. Staining rack
3. Slides or cover slips
4. Wright's stain
5. Buffer solution and distilled water

Cleaning Slides and Cover slips

New Slides

1. Wash with soap and water, rinse thoroughly and dry.
2. Soak a short time in 95 per cent ethyl alcohol.
3. Dry with smooth cloth leaving no fuzz on the slide.
4. Flame slides over a Bunsen burner.

Old Slides

1. Boil in 5 per cent sodium bicarbonate solution.
2. Wash with soap and water and rinse thoroughly.
3. Place in cleaning solution for 12 hours (see solutions, page 167)

4 Then treat as new slides

Cover slips

1 Same as for new slides but do not flame

Procedure

Slide Method

1 Puncture finger as for count
2 Take a clean slide and gently touch it to the drop of blood Do not touch the finger
3 Place the slide between the third finger and the thumb of the left hand with the drop of blood on the top surface
4 Take a second slide and place the narrow edge of the slide in front of the drop of blood with the spreader slide angled toward the right hand at a 30-degree angle
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4 Wash with distilled water Be sure to flood the stain from the preparation because pouring it off will cause a precipitate to be found on the smear Once there it cannot be washed off
5 Drain with the thin end of the preparation pointed upward
6 Air-dry
7 Cover slips must be mounted on a slide when dry

Counting

1 Check the preparation under 16 mm objective for distribution of cells
2 Under 1 8 mm objective count at least 100 white cells
3 Classify these according to the Schilling classification

Myelocytes	Lymphocytes
Juveniles	Monocytes
Bands	Eosinophils
Segmented	Basophils

In leukemias all immature cells must be classified

GIEMSA STAIN

1 *Fix blood film in methyl alcohol* for from 2 to 3 minutes
2 Place in freshly prepared stain for 30 minutes

GRAHAM S ALPHA NAPHTHOL PYRONINE STAIN (A PEROXIDASE STAIN)

Air dried smears are fixed in from 1 to 2 minutes in a freshly prepared mixture of 1 part formalin to 9 parts 95 per cent alcohol

Method

1 Wash with H O
2 Stain solution A from 4 to 5 minutes
3 Wash in running H O 15 minutes
4 Stain solution B for 2 minutes
5 Wash with H O
6 Stain with 0 5 per-cent aqueous methylene blue from ½ to 1 minute Wash

Nuclei of all cells Blue

Neutrophilic Granules Purplish red

Cytoplasm Blue

Erythrocytes From greenish yellow to pink

HEMOGLOBIN DETERMINATION

Haden Hausser Method

Materials and Equipment

1 Equipment for finger puncture
2 White pipette
3 Haden Hausser hemoglobinometer
4 1/N Hcl

Procedure

1 Puncture finger
2 Draw blood to 0 5 mark in white pipette
3 Dilute with 1/N Hcl to 11 mark of white pipette
4 Allow to stand 20 minutes
5 Remove first 2 drops from pipette and fill the hemoglobinometer chamber
6 Match the yellow colors and read the grams and per cent of hemoglobin

Sahli Hemoglobinometer

Materials and Equipment

1 Equipment for finger puncture
2 Sahli pipette 20 cu mm of blood
3 Sahli hemoglobinometer
4 *1/N Hcl*
5 Distilled water

Procedure

1 Fill the graduated tube of the hemoglobinometer with 1/N Hcl to the 10 mark
2 Puncture finger

3 Draw the blood to the mark 20 cu mm on the pipette
4 Place the tip of the pipette in the bottom of the tube and mix the blood thoroughly with the solution Rinse the pipette with the solution
5 Let stand for 10 minutes
6 Add distilled water drop by drop until the color matches the standard
7 The amount of solution is read off on the graduated tube It corresponds to per cent and grams of hemoglobin

PHOTO ELECTRIC METHOD
(Sheard Sanford)

Materials and Equipment

1 Equipment for finger puncture
2 Pipette to measure 0 1 cc of blood
3 0 1 per cent sodium-carbonate solution
4 Test tube volume 25 cc
5 Photo-electric hemoglobinometer

Procedure

1 Place 20 cc of 0 1 per-cent sodium carbonate solution in a tube
2 Puncture finger
3 Draw blood to mark in pipette 0 1 cc of blood
4 Place pipette in sodium carbonate and mix the blood with the solution Rinse the pipette This gives 1 200 solution of oxyhemoglobin
5 Read in photo-electric instrument that must be calibrated for hemoglobin

This method is the most accurate one for determination of hemoglobin It may vary with the instrument used

VOLUME INDEX

WINTROBE S HEMATOCRIT METHOD

Materials and Equipment

1 Equipment for venepuncture
2 Wintrobe hematocrit tube
3 Capillary pipette for filling the tube
4 Heller and Paul s anticoagulant (see solutions) (0 1 cc for every cc of blood)
5 Centrifuge

Procedure

1 Draw a little over 3 cc of blood from a vein in the usual manner
2 Place 3 cc exactly of blood in a tube containing 0 3 cc of anticoagulant and shake gently
3 Shake for 2 minutes Fill the Wintrobe tube with the oxalated blood to the 10 mark
4 Place in centrifuge for 20 or 30 minutes Take one reading at the end of 20 minutes and another at the end of 30 minutes If the readings are the same that reading may be accepted if not the tube must be placed in the centrifuge again and spun until 2 consecutive readings are the same Read the volume of packed red cells using the column of figures which starts with 1 at the bottom and ends with 10 at the top

Calculation

If the reading is 4 65 per 10 cc of blood then the P C V is 46 5 cc per 100 cc of blood The normal packed cell volume for women is 42 0 and for men it is 47 0

To calculate the volume index divide the per cent of red cells into the per cent of packed cells

Example
R B C 3 500 000 (Female patient)
P C V 32 0
Per cent R B C 35 × 2 = 70
Per cent packed-cell volume = 32 — 42 × 100 = 76
Volume Index 70 — 76 = 92
Normal volume index is 0 85 to 1 0

SEDIMENTATION RATE

Procedure

1 Collect blood as for hematocrit Fill Wintrobe tube (within 30 minutes after collecting the blood)
2 Record the fall of the cells at 15 minute 30 minute 45 minute and 60 minute intervals
3 Correct for anemia by use of correction chart

Normal Women 0-20 mm men 0-9 mm

COLOR INDEX

Calculation

Double the first two numbers of the red cell count and divide it into the per cent of hemoglobin

Example
R B C 3 500 000
Hemoglobin 11 Gm (71%)
Per cent R B C 35 × 2 = 70
C I 71 — 70 = 1 01
Normal color index is 0 9 to 1 04

MEAN CORPUSCULAR VOLUME (WINTROBE)

M C V is a simple method for estimation of the volume of the average red cell

$$\text{M C V} = \frac{\text{Volume of packed red cells (in cc per 1000 cc of blood)}}{\text{Number of red cells (in millions per cu mm)}}$$

Example
P C V 46 0
R B C 4 800 000

$$\text{M C V} = \frac{46 \times 10}{4\ 8} = 95.8 \text{ cubic}$$

microns
Normal 80-94

MEAN CORPUSCULAR HEMOGLOBIN (WINTROBE)

M C H is a means of expressing the amount of hemoglobin in the average red cell

$$MCH = \frac{\text{Amount of hemoglobin (in grams per 1000 cc of blood)}}{\text{Number of red cells (in millions per cu mm)}}$$

Example
R B C 4 800 000
Hemoglobin 14 Gm (91%)

$$\text{M C H} = \frac{14 \times 10}{4\ 8} = 29\ 1 \text{ micro-}$$

micrograms of hemoglobin
Normal 27 32

MEAN CORPUSCULAR HEMOGLOBIN CONCENTRATION (WINTROBE)

M C H C is the amount of hemoglobin in the average red cell expressed in percentage

$$\text{M C H C} = \frac{\text{Amount of hemoglobin (in grams per 100 cc of blood)}}{\text{Vol of packed red cells (in cu cm per 100 cc of blood)}}$$

Example

Hemoglobin 14 Gm (91%)

PCV 46 0

$$MCHC = \frac{14}{46} \times 100 = 30\ 4 \text{ per cent}$$

Normal 33-38

MEAN CORPUSCULAR DIAMETER (HADEN HAUSSER ERYTHROCYTOMETER)

The erythrocytometer is a simple instrument for measuring rapidly the mean diameter of red cells It is based on the principle that light passing through a film or other preparation of blood is diffracted at the edges of the individual blood cells and varies with the size of the cells and the distance from the source of light The source of error in this method is in not having the preparation thin enough One must have a very thin evenly smeared blood film The cells should not overlap but should just touch each other A more accurate but very tedious method is actual micrometer measurement of 1000 red cells and plotting a curve (Price Jones Method)

Procedure

Place the blood film in the slot just above the stage of the erythrocytometer Turn the light on by pressing the button and adjust the hand wheel When it is adjusted to read the spectrum will be clearly defined and the inner red ring will coincide with the inner set of four apertures The mean diameter is then read directly from the scale on the hand wheel

FRAGILITY TEST (SANFORD'S METHOD)

Materials and Equipment

1 Equipment for venepuncture—must be dry
2 Two sets of 12 tubes each numbered from 14 to 25 and racks
3 0 5 per-cent saline solution
4 Freshly distilled water
5 Capillary pipette

Procedure

1 Using the capillary pipette drop as many drops of 0 5 per-cent saline solution in the tubes as the number on the tube indicates
2 With the same pipette add drops of distilled water to every tube until the total number of drops in each tube is 25 The angle of the capillary pipette should be consistent
3 Withdraw about 2 cc of blood by venepuncture Take care to cause no hemolysis while withdrawing the blood
4 Using a 23-gauge needle place one drop of blood in each of one set of 12 tubes If oxalated or citrated blood is used the cells must be washed with physiologic saline and a 50-per-cent solution made with the same Place one drop in each of the 12 tubes
5 Using the other set of 12 tubes set up a control of normal blood using the same technic as that used on the patient

Calculation

The percentage strength of the solution of sodium chloride in each tube is equal to the number on the

tube multiplied by 0 02 The test should be read in 2 hours and again in 24 hours

Normal Initial hemolysis 0 44 0 42
Complete hemolysis 0 34 0 32

PLATELET COUNT (FONIOS SMEAR METHOD)

Materials and Equipment

1 Equipment for finger puncture
2 Wright s stain (see stains)
3 14 per cent aqueous solution of magnesium sulfate
4 Material for red count
5 Pipette slides and microscope

Procedure

1 Collect an erythrocyte count
2 Dry finger and place a small drop of magnesium sulfate over the wound
3 Press the finger gently so that the blood will rise through the mag nesium sulfate This keeps the platelets from clumping
4 Make a blood smear from this drop of blood
5 Count the erythrocyte count
6 Stain smear with Wright s stain as would be done with a differen tial smear
7 Count 1000 red cells and the plate lets seen while counting them

Calculation

Multiply the number of platelets counted by the first four numbers of the red count

Example

R B C 4 200 000
Platelets 72
4 200 × 72 = 302 400 platelets per cu mm
Normal 250 000 350 000

RETICULOCYTE COUNT

Materials and Equipment

1 Equipment for finger puncture
2 Brilliant cresyl blue stain (see stains)
3 Slides cover slips and microscope

Procedure

1 Place 1 drop of brilliant cresyl blue on a slide and smear it as a blood smear
2 Allow to dry and then polish the slide lightly with a clean sponge There should then be an even spread of the stain over the slide
3 Puncture the finger and wipe with a dry sponge
4 Collect a very small drop of blood on a cover slip and invert it on the slide The maximum spread should be reached without the blood s reaching the edges of the cover slip Preparation must be rather thin
5 Allow to stand for 10 minutes
6 Count 1000 red cells and the retic ulocytes seen in these 1000 cells

Calculation

Divide the number of reticulocytes counted by 10 This gives the per cent of reticulocytes

Example

Reticulocytes in 1000 R B C 23
23 ÷ 10 = 2 3 per cent reticulo cytes
Normal 0 5 1 0 per cent

SICKLE CELL PREPARATION

SLIDE METHOD

Materials and Equipment

1 Equipment for finger puncture
2 Coverglass and slide

3 Small rubber band
4 Petrolatum
5 Microscope

Procedure

1 Place rubber band round proximal phalanx of finger for from 1 to 2 minutes
2 Puncture finger
3 Place a small drop of blood on the cover slip and quickly invert on the slide
4 Ring the cover slip with petrolatum
5 Examine immediately and again in 24 hours

BLEEDING TIME (DUKE METHOD)

Materials and Equipment

1 Equipment for finger puncture
2 Filter paper
3 Watch

Procedure

1 Incise the skin of the lobe of the ear Cut should be about 0 2 cm long and 0 1 cm deep
2 Note time the first drop of blood appears
3 Blot with filter paper at intervals of 30 seconds until the bleeding ceases
4 The interval between the first and the last drop is the bleeding time

Normal 1 3 minutes

COAGULATION TIME

Capillary Tube Method

Materials and Equipment

1 Equipment for finger puncture
2 Finely drawn capillary glass tubes
3 Watch

Procedure

1 Puncture the finger and fill the capillary tube with blood
2 Note time when blood appears
3 Holding the tube between the thumb and the index finger of both hands gently break the tube every 30 seconds until a strand of fibrin appears
4 The interval between the appearance of the blood and the appearance of the fibrin strand is the coagulation time

Normal 1-6 minutes

Venepuncture Method (Lee & White)

Materials and Equipment

1 Equipment for venepuncture
2 Test tube (8 mm in diameter)
3 Watch

Procedure

1 With a dry sterile syringe puncture the vein and withdraw 1 cc of blood
2 Note time that blood appears in the syringe
3 Remove the needle and place blood in the test tube
4 Tilt the tube at intervals until the tube can be inverted without letting the blood flow out coagulation is complete
5 The interval of time between the appearance of the blood in the syringe and the point at which coagulation is complete is the coagulation time

This method is probably more accurate than the capillary tube method

Normal 5-10 minutes

CLOT RETRACTION

Save the tube from Lee & White coagulation time Clot should begin *to retract in 2 hours* Retraction should be complete in 24 hours with a firm and well formed clot Lack of retraction is associated with a platelet deficiency

CAPILLARY RESISTANCE TEST OF RUMPEL LEEDE

Materials and Equipment

1 Blood pressure cuff or tourniquet
2 Skin marking pencil

Procedure

1 Examine the patient s arm for petechiae Mark them with a skin pencil
2 Place the tourniquet on the arm of the patient for 5 minutes
3 Examine the arm for new petechiae

If there is an increase in the number of petechiae or it they appear the test is considered positive

PROTHROMBIN TIME (METHOD OF ZIFFREN OWEN HOFFMAN AND SMITH)

Materials and Equipment

1 Equipment for venepuncture.
2 Two small test tubes
3 Stop watch
4 Thromboplastin

Procedure

1 Make up thromboplastin (Winthrop Niphanoid)
2 Place 0 1 cc. exactly of thromboplastin in each of the small test tubes
3 Take these tubes to the bedside with you
4 Make venepuncture and place 0 9 cc exactly of *whole blood in the* tube containing the thromboplastin Mix
5 Note the time and then gently *tilt the tube until the clot is* formed
6 *Record* the clotting time of the patient
7 Run a similar test on a normal person

Calculation

$$\text{Clotting activity in per cent of normal} = \frac{\text{Clotting time of normal}}{\text{Clotting time of patient}} \times 100$$

UROBILINOGEN

Procedure

1 *Use only fresh* urine *as urobilinogen* is broken down on standing
2 *To 10 cc of urine add 1 cc of* Ehrlich s reagent (see solutions)
3 Let stand from about 5 to 10 minutes A red color indicates the presence of urobilinogen
4 If a positive test is obtained then a quantitative test *should be* run the test being repeated in the dilution 1 10 1 20 etc

Normal Test may be positive in dilutions up to 1 20

ICTERUS INDEX

May be done by the photo-electric method by Duboscq colorimeter or by comparing *with standards For* practical purposes the LaMotte Pig

ford icterus index comparator is available

Materials and Equipment

1 Equipment for venepuncture
2 Icterus index comparator
3 Distilled water
4 Centrifuge
5 Clean test tube

Procedure

1 Collect about 5 cc. of blood by venepuncture, using dry syringe Care should be taken to prevent hemolysis
2 Place in clean test tube and allow to clot.
3 Ring the clot and spin down in the centrifuge If the serum shows evidence of hemolysis or has fat in it the determination will not be accurate
4 Place serum in matched tube to serum mark and add distilled water to the second mark Compare with the set of standards and read the icterus in units
   Normal 3-6 units

MALARIA PARASITES

Thick Smear

1 Place 1 large drop of blood on the end of a slide
2 Stir with an applicator stick until fibrin clings to stirrer (1 minute)
3 Allow to dry and dehemoglobinize in water
4 Stain with freshly diluted Giemsa stain and examine for parasites under 1 8-mm objective Species may be determined by examining a thin smear prepared as for differential leukocyte count.

ASPIRATED STERNAL MARROW

About 2 cc of material should be obtained by aspiration from the sternum and used in the following ways Sternal aspiration should be done only by a physician

Slide and Cover Slip Method

Using the fresh unoxalated marrow prepare slides and cover slips as would be done for peripheral blood Care must be taken so that the young cells will not be torn up in making the smear In staining these slides it is usually best to double all the times used in staining

Leukocytic Cream Method

With the end of a Bard Parker blade size 11 place a very small amount of heparin in a tube Add to this 1 cc of the material obtained by aspiration Shake the tube gently for 2 minutes Place in a Wintrobe tube as would be done for sedimentation rate Centrifuge at 500 R P.M for from 5 to 10 minutes Make smears from the heavy creamy layer on top Treat as above

Impression and Tissue Material

Place the remaining material on a large glass slide Using care gently pick up a small piece of marrow and make an imprint of it on a slide This should be stained the same as the other slides

Then as rapidly as possible push together the little flecks of marrow Allow the blood to begin to clot and then transfer this preparation to a small piece of filter paper After a

few seconds drop it into whatever fixative is used for tissue sections and treat it as a histologic section

Relative Number of Nucleated Cells in Normal Bone Marrow

Myeloblasts	0.5 5.0
Premyelocytes (undifferentiated A and B)	1.0 8.0
Myelocytes Neutrophilic	5.0 19.0
Myelocytes Eosinophilic	*0.5 3.0*
Myelocytes Basophilic	0.0 0.5
Metamyelocytes (juvenile forms)	13.0 32.0
Neutrophils (non segmented)	15.0-30.0
Polymorphonuclear neutrophils	7.0-30.0
Polymorphonuclear basophils	0.0- 0.7
Polymorphonuclear eosinophils	0.5 4.0
Lymphocytes	3.0-17.0
Plasma cells	0.0- 2.0
Monocytes	0.5 5.0
Reticulum cells	0.2 2.0
Megakaryocytes	0.03 3.0
Megaloblasts	0.0- 2.0
Pronormoblasts (macroblasts)	1.0- 8.0
Normoblasts (basophilic polychromatophilic and acidophilic)	7.0-32.0

HETEROPHIL ANTIBODY TEST

Materials and Equipment

1 Equipment for venepuncture
2 Rack of 12 small tubes (75 × 10 mm)
3 Solution of 0.9 per-cent sodium chloride
4 2 per-cent washed sheep cells (at least 1 day old and not more than 1 week old Wash the cells 3 times with 0.9 per-cent sodium chloride)
5 *Three pipettes 1 cc*
6 56° water bath

Procedure

1 Collect about 5 cc of blood allow to clot and remove the serum from it
2 Inactivate the serum for 30 minutes at 56° C
3 Set up rack of 12 tubes and number them
4 In the first tube place 0.4 cc of *salt solution and 0.25 cc into each* of the others
5 Place 0.1 cc of the inactivated serum into the first tube mix and transfer 0.25 cc to the second tube etc discarding the 0.25 cc removed from the eleventh tube so that the twelfth tube is a control Dilutions are 1 5 1 10 etc
6 Add 0.1 cc of 2 per cent washed sheep cells to each tube and mix Dilutions are now 1 7 1 14 etc
7 Leave at room temperature for 2 hours Read after shaking until the cells become resuspended Place in icebox overnight and check reading in the morning

A titer over 1 64 is indicative of a positive test

Rh TYPING

Slide Method

Procedure

1 The completed reaction takes place in a short time therefore not more than from 5 to 10 tests should be run at any one time

2 Red cell suspension Place 2 drops of blood from finger or ear puncture into 0 5 cc of physiologic saline containing 1 per cent sodium citrate (10-per-cent cell suspension)

3 Place 1 drop of blood cell suspension on a clean glass slide and 1 drop of anti Rh serum next to it Mix both drops over an area of about ¾ of an inch Very gently tilt the slide back and forth once Vigorous motion will break up the clumps and make a positive test appear negative

4 At the end of 3 minutes pick slide up and very gently tip back and forth 2 or 3 times Observe for macroscopic clumping of erythrocytes while keeping the slide in slight motion until 6 minute period has ended Clear cut clumping of cells is present in positive tests at the end of 6 minutes

5 All readings must be macroscopic and it is highly desirable to run parallel known positive and negative controls

The technic outlined may be used with any potent Rh antisera

ANTI Rh AGGLUTININS AND BLOCKING ANTIBODIES

Drop of serum to be tested is mixed with a drop of Group O Rh positive red cells suspended in physiologic saline and the mixture is incubated in a water bath No agglutination of the cells indicates the absence of anti Rh agglutinins One drop of potent human anti Rh agglutinating serum is then added and the mixture is reincubated Strong agglutination should be present if the tested serum does not contain anti Rh agglutinins and no or very weak agglutination if Rh blocking antibodies are present The anti Rh blocking antibodies prevent the usual reaction of Group O Rh positive cells with known potent anti Rh agglutinating serum Therefore it is evident that Rh blocking antibodies have prevented anti Rh agglutinating serum from reacting with the Group O Rh positive cells in producing strong clumping The blocking test has proved a useful supplement to the usual agglutination test for Rh sensitivity If anti Rh agglutinins are present test tube dilutions should be done

BLOOD GROUPING

Procedure

1 Place one drop of Group A serum on one end of a slide and a similar quantity of Group B serum on the other end of the slide

2 Mix an equal amount of a 2 per cent red-cell suspension with each Be sure either to flame the loop between each transfer or to use a different dropper

3 Place slide on a damp towel and cover with a Petri dish Allow to stand 30 minutes

4 Read

(A) Agglutination on both sides —Type AB
(B) Agglutination by type B serum —Type A
(C) Agglutination by type A serum —Type B
(D) No agglutination —Type O

CROSS MATCHING

Procedure

1 Slide is marked so that one end contains donor s cells plus patient s *serum* while the *other* end has donor s serum plus patient s cells (DC+PS and DS+PC)

2 On the end of the slide so marked place one loop full of patient s serum and mix one loop full of donor s cells

3 On the other end of the slide place one loop full of donor s serum and one loop full of patient s cells (Be sure to flame the loop between each transfer)

4 Place slide on damp cloth and cover with Petri dish Allow to stand 60 minutes

5 Read

(A) No agglutination = Compatible cross match

(B) Rouleaux formation = Compatible cross match

(C) Any agglutination = Cross *match not compatible*

(NOTE Patient s cells are a 2 per cent suspension in physiologic saline)

AUTO AGGLUTINATION

Auto-agglutination of the erythrocytes will show up as clumps of red cells in the diluting fluid This will be noted in the counting chamber as these cells are usually evenly distributed without any clumps If such agglutination is found a test tube titer should be run at icebox incubator and room temperatures

STAIN PREPARATIONS

Wright s Stain

Wright s powder stain	0.3 Gm
Glycerin	3 0 cc
Methyl alcohol absolute acetone free	97 0 cc

Mortar the Wright s powder and the *glycerin Add the methyl alcohol* Place in a 37° C incubator to hasten oxidation process May use in a few days It improves with age

Giemsa Stain

Stock solution

Giemsa powder stain	0.3 Gm
Glycerin	25 0 cc
Methyl alcohol absolute acetone free	25 0 cc

Dilute stain (ready for use)

Stock solution	1 0 cc
Distilled water to	10 0 cc

Brilliant Cresyl Blue

Brilliant cresyl blue powder	1 0 Gm
Methyl alcohol absolute acetone free	100 0 cc

Graham s Alpha Naphthol Pyronine

Solution A

Alpha naphthol	*1 0 Gm*
Alcohol 40 per cent	100 0 cc
Distilled water	0 2 cc

Solution B

Pyronine	0 1 Gm
Aniline	4 0 cc
Alcohol 40 per cent	*96 0 cc*

Dissolve pyronine in alcohol add aniline

Methylene Blue

Saturated alcoholic solution of methylene blue	*30 0 cc*

1:10,000 aqueous solution of KOH 100.0 cc

Gower's Solution (Red cell Diluting Fluid)

Sodium sulfate	12.5 Gm
Glacial acetic acid	35.3 cc
Distilled water to	200.0 cc

Physiologic Saline (Red cell Diluting Fluid)

Sodium chloride C.P.	8.5 Gm
Distilled water to	1000.0 cc

Hayem's Solution (Red cell Diluting Fluid)

Mercuric chloride	0.5 Gm
Sodium sulfate	5.0 Gm
Sodium chloride	1.0 Gm
Distilled water to	200.0 cc

Hydrochloric acid Solution (White cell Diluting Fluid)

Hydrochloric acid concentrated	1.0 cc
Distilled water to	100.0 cc

Acetic acid Solution (White cell Diluting Fluid)

Glacial acetic acid	4.0 cc
Distilled water to	100.0 cc
Gentian violet to color	

Anticoagulant (Heller and Paul)

Potassium oxalate	0.8 Gm
Ammonium oxalate	1.2 Gm
Distilled water to	100.0 cc

Buffer Solution

Potassium phosphate (monobasic)	1.65 Gm
Sodium phosphate (dibasic)	3.2 Gm
Distilled water to	1000.0 cc

Ehrlich's Reagent

Hcl concentrated	20.0 cc.
Distilled water to	100.0 cc
Dimethyl amino benzaldehyde (para)	2.0 Gm

23

Summary of Hematologic Findings

HEMATOLOGIC FINDINGS IN VARIOUS DISEASES AND CONDITIONS

In the following section an attempt is made to summarize briefly the hematologic findings in diseases of all types It is realized that this can not be done accurately since certain diseases such as typhoid fever may be ushered in by leukopenia with the blood findings returning to normal and then later in the disease there may be a leukocytosis with relative lymphocytosis and in other stages a monocytosis Most virus diseases are ushered in by periods of leukopenia and this is also true of the so called diseases of childhood

The type of cellular reaction in the blood reflects as a rule the underlying cellular changes that are taking place in the fixed tissues at the site of infection Furthermore the hematologic response in the same disease may vary considerably in different individuals It is always likely to be more marked in children than in adults The cellular response to various types of infections depends upon a large number of factors these including the capacity of the patient to respond by marrow or other cellular output the severity of the infection the amount of tissue and what tissues are involved and the particular time during the disease that the blood samples may be removed These considerations should be borne in mind in the evalution of blood findings in any disease

Abscess of Liver

Usually a marked neutrophilic leukocytosis the degree dependent upon the extent of the process

Achrestic Anemia

A rare type of macrocytic hyperchromic anemia with a blood picture the same as that of pernicious anemia It differs from the latter in that there is no achlorhydria and that it is refractory to treatment with liver

Actinomycosis

There is usually a neutrophilic leukocytosis in the acute stage of the disease As the condition becomes chronic the cells fall to a normal level A hypochromic anemia usually develops in both acute and chronic forms

Acute Leukemias (Acute Leukosis)

In the early stages there is little anemia but as the disease progresses to the late stages the anemia is pro

found There is some variation in size and in shape of the cells also polychromatophilia an occasional nucleated cell a rare megaloblast and low hemoglobin The blood platelets are nearly always reduced so that hemorrhagic disorders are very common The leukocyte picture is characteristic since a large percentage of the cells are blast forms This establishes the diagnosis of acute leukemia but to differentiate myeloblasts from lymphoblasts or monoblasts is a difficult matter The leukocyte count is usually elevated but not necessarily to extreme degrees as in the chronic forms At times an aleukemic phase is present Most of the acute leukemias are myeloid with the cell predominating the myeloblast (micromyeloblast normomyeloblast or macromyeloblast)

Addison s Disease

The blood picture is usually normal but a leukopenia may occasionally be seen A macrocytic anemia may exist Occasionally there is an eosinophilia or a relative lymphocytosis The blood picture is not sufficiently characteristic to aid in diagnosis

Allergy

Most allergic disorders produce one hematologic reaction in common and that is eosinophilia The following allergic disorders may be accompanied by increased eosinophils Hay fever asthma urticaria angioneurotic edema eczema parasitism certain other forms of gastro intestinal disorders and some forms of cystitis and arthritis In children rhinitis sinusitis nasopharyngitis pharyngitis tonsillitis laryngitis tracheitis and bronchitis may be on an allergic basis and give rise to an eosinophilia

Amebiasis

There is usually a marked neutrophilic leukocytosis The hematologic picture is otherwise unaltered unless some complication develops and then there is a higher leukocytosis As the disease becomes chronic an anemia develops This is usually of a hypochromic type but in prolonged cases a macrocytic hyperchromic anemia may develop

Ancylostomiasis (Hookworm Anemia)

In severe infestations there is a marked anemia of the hypochromic microcytic type The reticulocytes are low There is a characteristic eosinophilia which reaches a high level Infestation by other intestinal parasites usually results in a similar picture

Angina Ludwig s

There is a moderate to a severe neutrophilic leukocytosis also anemia in the later stages

Angioneurotic Edema

See Allergy

Anthrax

There is usually leukopenia in the early stage but in the latter phases there may be leukocytosis with a neutrophilic left shift Sometimes anthrax bacilli may be found in the blood stream and seen on stained films

Aplastic Anemia Primary Idiopathic

There is a marked decrease in the

erythrocytes the thrombocytes and the granulocytic leukocytes The anemia is normocytic and normochromic and the erythrocytes reach extremely low levels The hemoglobin is decreased in proportion to the erythrocytes The color and the volume indices are normal There is no evidence of active erythropoiesis The granulocytes are either absent or decreased so that there is a relative lymphocytosis The platelets may be entirely absent in the smear

Aplastic Anemia Secondary (An Aplastic Anemia of Known Etiology)

1 Benzene poisoning The blood picture is variable depending on the extent of exposure In the usual case there are a profound granulocytopenia and a relative lymphocytosis A moderate or a severe anemia may develop This is progressive developing into the aplastic type with a fatal termination The leukocytes vary considerably so that at one time the count is normal and at another time there is a neutropenia In mild cases with a neutropenia and an anemia there may be evidence of active erythrogenesis as the leukocytes return to normal

2 Arsenic poisoning This is rare during the administration of arsenicals The anemia is similar to the idiopathic aplastic type except that the prognosis is better In arsenical dermatitis there is an extreme eosinophilia with a leukocytosis

3 Radiation The blood picture is variable A mild anemia is not uncommon There may be an aplastic type of anemia with severe leukopenia and even leukemia has been suspected The blood picture is usually characterized by erythropenia thrombocytopenia and leukopenia or any combination of these

4 In other diseases Aplastic or hypoplastic anemia with blood pictures similar to the above may develop in the following Terminal stage of leukemia (myeloid type) overwhelming sepsis bismuth salicylate poisoning radium poisoning polonium poisoning poisoning with lye saponin arsenic collargol bichloride of mercury and salvarsan in typhus in sprue and in arthritis in senility and at the menopause after prolonged hemorrhages in osteosclerosis in bone marrow tumors and in pernicious anemia in relapse

Appendicitis

There is a moderate leukocytosis with a granulocytic shift to the left In some cases however the total leukocyte count may be normal or below normal and the important change is the shift to the left A normal leukocyte count with a marked shift to the left has as much diagnostic value as a pronounced leukocytosis A leukopenia is an unfavorable sign since it indicates a marked leukocyte accumulation at the site of infection or an inability of the marrow to produce cells This same type of blood picture is seen in other pyogenic abdominal infections Peritonitis and abscess formation usually give rise to a higher leukocytosis than simple appendicitis Anemia rarely develops unless the illness is prolonged

Arachnoidism (Spider bite Poisoning)

The bite of the black widow spider frequently produces a moderate elevation in the total leukocyte count and a marked eosinophilia The period of leukocytosis usually precedes the eosinophilia

Arsenic Poisoning

See Aplastic Anemia Secondary

Arthritis Rheumatoid

In many patients there is a moderate degree of leukocytosis with a neutrophilic left shift The sedimentation rate of red cells is increased In the more chronic forms these findings subside

Asiatic Cholera

See Cholera Asiatic

Asthma

In most cases there is eosinophilia without a significant leukocytosis unless there is a complication such as bronchitis or bronchopneumonia Also see Allergy

Atrophy Acute Yellow

See Cirrhosis of the Liver

Banti s Disease (Splenic Anemia)

The blood picture is neither characteristic nor constant In many cases there is a definite neutrophilic leukopenia with a relative lymphocytosis The leukopenia may be quite marked Platelets may or may not be decreased Bleeding and coagulation times are normal There is usually a hypochromic anemia and because of liver damage it may be macrocytic If the patient has bled considerably from esophageal varices the anemia may be severe As a rule the leukocytes are mature

Barlow s Disease

See Infantile Scurvy

Benzene Poisoning

This chemical does not produce a typical blood picture as was formerly believed Ordinarily there is a decrease in the number of erythrocytes granulocytes and thrombocytes In some the anemia is more pronounced in others the leukopenia is the chief feature, so that the disease may be confused with true agranulocytosis The blood picture is variable and an occasional patient may finally develop leukemia Polycythemia anemia leukocytosis leukopenia leukemia or leukemoid pictures eosinophilia megalocytosis and microcytosis have all been reported In chronic cases there is an aplastic type of anemia with granulocytopenia

Also see Aplastic Anemia Secondary

Boeck s Sarcoid

See Sarcoidosis

Bronchopneumonia

The blood picture is not typical but there is almost always a moderate leukocytosis As a rule the total count is not as high as in lobar pneumococcal pneumonia Children are likely to show wide variations in the total leukocyte count When influenza with leukopenia becomes complicated by bronchopneumonia (coccal) there is a moderate leukocytosis Anemia does not develop unless there is a severe and a prolonged illness or unless the patient was treated

erythrocytes the thrombocytes and the granulocytic leukocytes The anemia is normocytic and normochromic, and the erythrocytes reach extremely low levels The hemoglobin is decreased in proportion to the erythrocytes The color and the volume indices are normal There is no evidence of active erythropoiesis The granulocytes are either absent or decreased so that there is a relative *lymphocytosis The platelets may be* entirely absent in the smear

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with a drug capable of producing hemolytic anemia

Brucellosis

See Undulant Fever

Bubonic Plague

The leukocyte count is normal or perhaps leukopenic in early stages and there is leukocytosis in the stage of suppuration of buboes The plague organisms are sometimes demonstrable in stained blood films

Buerger s Disease

See Thromboangiitis Obliterans

Burns

The blood picture depends upon the severity of the burn and the amount of surface tissue involved In severe cases there is concentration of the blood because of fluid loss so that the red cell count may be considerably elevated In these cases there is also extreme leukocytosis with a marked shift to the left This blood picture returns to normal as hydration is restored to its proper level After this an anemia may be found to exist

Carbon monoxide Poisoning

The blood is bright cherry red Carbon monoxide can be demonstrated by spectroscopic examination

Carcinoma of Stomach

See Stomach Carcinoma of

Celiac Disease (Idiopathic Steatorrhea) (Gee s Disease)

There is often a macrocytic hyperchromic anemia simulating that of pernicious anemia in all respects However in some instances the anemia may be of the microcytic hypochromic type Erythroblastic or hemolytic anemia is quite rare

Chickenpox

The erythrocytes are usually normal There is leukocytosis caused by increased lymphocytes During the late stage there may be an eosinophilia In severe cases there may be a leukemoid reaction

Childhood Physiologic Anemia of (First Month)

At birth the red cells are higher than normal but after a few weeks there is a gradual decrease in both erythrocytes and hemoglobin Frequently the hemoglobin falls much lower in proportion to the erythrocytes so that a pronounced hypochromia exists The blood picture returns to a normal level within a short time Later in childhood a mild hypochromic anemia from an iron deficiency may develop

Chloroma (Chloroleukemia)

This seems to be an atypical type of leukemia with the blood picture characterized by large numbers of immature granulocytic cells Usually the picture is the same as in chronic myelogenous leukemia with variable total leukocyte levels and at times there may be a leukopenia Anemia develops to a severe degree and there is marked evidence of erythrogenesis

Chlorosis

This disease is characterized by severe anemia a low color index mild leukopenia with relative lymphocytosis and an increased number of platelets during the recovery phase Leukopenia is not invariable If the

anemia is marked there may be anisocytosis and poikilocytosis The *erythrocytes appear small in stained* smears and the cell volume is below normal with the picture of microcytic hypochromic anemia

Cholecystitis

There is usually neutrophilic leukocytosis in the acute form and there is very little blood change in the more chronic types Associated cholelithiasis shows an elevated icterus index increased bilirubin in the blood plasma and usually a positive van den Bergh reaction

Cholera

Since this disease is characterized by passage of large numbers of watery stools the patient is dehydrated and concentration of the blood results Therefore the red-cell count and the hemoglobin are elevated Later however an anemia usually develops The neutrophilic leukocyte count is high from the beginning

Cirrhosis of the Liver

In many instances there is a macrocytic hyperchromic anemia similar to that seen in pernicious anemia The degree of anemia varies but usually it becomes profound after rupture of esophageal varices Leukopenia with a relative lymphocytosis frequently accompanies the macrocytic anemia In other conditions such as acute toxic hepatitis acute yellow atrophy obstructive jaundice and extensive secondary carcinoma of the liver *there is likely to be a macrocytic anemia* Suppurative hepatic processes call forth a neutrophilic response. A simple hypochromic anemia rather than a macrocytic type, is probably more common in obstructive jaundice.

Colitis Ulcerative

Characteristic hematologic changes are not found but in active phases a definite neutrophilic leukocytosis and anemia prevail The leukocytosis may be quite marked when the patient is having episodes of fever There is variable anemia in nearly all cases It is usually hypochromic with only a slight erythrocyte decrease, but it may be a definite macrocytic type not unlike that of pernicious anemia

Cooley s Erythroblastic Anemia

There is nearly always a moderate to a severe anemia with color index normal Nucleated erythrocytes and reticulocytes appear in large numbers and there are anisocytosis poikilocytosis and polychromatophilia in varying degrees There is usually a marked leukocytosis with immature cells of the myeloid series to such an extent that the picture may be confused with leukemia In some cases the leukocyte count may be normal The platelets are usually normal The icterus index usually is slightly elevated As a rule urobilinogen is found in the urine and the stools It is a typical hemolytic anemia

Coronary Thrombosis

There is usually a moderate neutrophilic leukocytosis with a shift to the left In occasional instances the leukocyte count may be extremely high It subsides with healing and fibrosis Later there may be a secondary polycythemia when cardiac function has been poor over a long

period Conversely, if there is an associated poor renal function a secondary anemia may be present

Coryza, Acute (The Common Cold)

In the early stages of acute coryza there is little or no change in the blood findings In the late stages with bacterial invasion there may be a slight to a moderate leukocytosis with a mild left shift of neutrophils

Cretinism

See Hypothyroidism

Dengue

A marked leukopenia develops early the granulocytes being decreased so that there is a slight relative lymphocytosis During the convalescent stage there is usually an increase in monocytes in lymphocytes and in eosinophils

Dermatitis Exfoliative (Arsenical)

There is usually a typical blood picture consisting of a moderate leukocytosis and a pronounced eosinophilia

Diabetes Mellitus

No typical blood picture exists and if the disease is well controlled no changes are to be expected However a macrocytic anemia or a slight hypochromic anemia may be present During periods of acidosis there is a moderate leukocytosis and an increase in the erythrocytes takes place Fatty acids in the acidotic state may cause the leukocytosis or dehydration may be the cause If complications such as gangrene or carbuncles develop then there is a pronounced rise in the leukocyte count with a shift to the left

Diphtheria

Leukocytosis develops early and may be extremely high with myelocytes in the peripheral blood On rare occasions a leukopenia exists The red cells are usually not affected, but occasionally a rather severe anemia may develop rapidly

Diphyllobothrium Latum Anemia (Fish Tapeworm Anemia)

Infestation with this parasite very often gives rise to a macrocytic hyperchromic anemia which simulates pernicious anemia even with blood crises After treatment with liver the anemia may become hypochromic or microcytic In many cases the anemia is a hypochromic microcytic one from the beginning Eosinophilia is marked and there is leukocytosis to a variable degree

Drugs Causing Leukocytosis

See Leukocytosis Due to Drugs

Dysentery, Amebic

See Amebiasis

Dysentery Bacillary

The leukocyte count may be normal or slightly elevated In the chronic types anemia may develop This may be either the macrocytic or the microcytic hypochromic type

Eclampsia

The blood picture is neither characteristic nor constant but a moderate neutrophilic leukocytosis is nearly always present Anemia is not an outstanding feature but it does oc

cur in some cases Occasionally a slight eosinophilia may be seen

Empyema

There is usually a marked neutrophilic leukocytosis The degree depends upon the type of invading organism and the extent of the process

Encephalomyelitis Equine

There is always a moderate neutrophilic leukocytosis

Endocarditis Acute

Organisms (coccal) producing this disorder elicit a very marked leukocytosis In overwhelming infections there may be a leukopenia this depending probably on the rate of migration of cells to the infected areas A profound anemia develops if the patient lives long enough the anemia being of the hypochromic and microcytic type This same blood picture usually is seen in septicemia of more general acute types It is not uncommon to see a leukemoid reaction sometime during the illness When the causative organism is the hemolytic streptococcus the anemia is more severe and develops more rapidly

Endocarditis Subacute Bacterial

Marked leukocytosis is rare The total count is only moderately elevated However the blood count may remain within normal limits and become elevated only during embolic manifestations Most patients show some monocytosis Anemia usually develops early and is a progressive one In the early stages the anemia is hypochromic but later may become normochromic or on rare occasions macrocytic. The platelets are not affected

Enterogenous Cyanosis

If the reaction is caused by a drug there may be a hemolytic anemia of varying degree with the usual signs of cell destruction Usually however the only significant finding is the diagnostic color band seen in the spectroscope for sulfhemoglobinemia or methemoglobinemia

Eosinophilia Familial

This is a rare condition Several families have shown unexplained eosinophilia in members The total leukocyte count is usually normal.

Erysipelas

There are usually a moderate leukocytosis with a neutrophilic left shift and a hypochromic anemia in the latter stage of the disease

Erythroblastosis of the Newborn (Icterus Gravis Neonatorum)

This is characterized by a hemolytic anemia showing large numbers of immature red blood cells and many reticulocytes in the peripheral blood During the most active phase there is an erythroblastosis with all types of young red cells During the recovery period an eosinophilia may develop Marked leukocytosis with a shift to the left is almost always present Because of excessive cell destruction the icterus index is high

Exanthem Subitum

There is usually a neutropenia with a relative lymphocytosis However the few neutrophils present are

quite likely to be of the more immature types Occasionally plasma cells are present As the disease subsides the total count returns to a normal level and in many cases in the late stages there is a slight in *crease in eosinophils*

Familial Eosinophilia

See Eosinophilia Familial

Felty s Syndrome

This syndrome characterized by splenomegaly and arthritis usually shows a mild neutropenia

Fever Therapy

The blood picture after artificial fever therapy seems to be rather constant There is a neutrophilic leukocytosis of varying degree with nearly all cases showing an average rise of from 6000 to 7000 leukocytes per cu mm within a period of from three to seven hours (Krusen) However after treatment has been discontinued there is a pos febrile rise over a period of about 20 hours and the leukocyte count may reach a level of 40 000 per cu mm With this neutrophilic leukocytosis there is a *shift* to the left

Hemoconcentration is not seen unless the patients go into shock in which case there would be an increase in the erythrocyte count in hemoglobin and in hematocrit

Filariasis

Nearly all cases show some degree of leukocytosis and the increase seems to affect all cells Eosinophilia commonly occurs with a very high percentage in some cases The embryos *can be found* in the blood in most cases by studying fresh unstained blood in the middle of the night

Fish Tapeworm Infestation

See Diphyllobothrium Latum Anemia

Food Poisoning

See Salmonella *Infections*

Gas Gangrene

There is a marked leukocytosis with a predominance of cells of the granulocytic series *A very profound* hemolytic anemia may develop rapidly and signs of active erythropoiesis may become evident quite early

Gastro intestinal Dysfunction

Anemia frequently develops after *partial or complete gastrectomy* gastro-enterostomy removal of the upper duodenum resection of a large part of the small intestine entero-enterostomy gastrocolic fistula and other surgical operations on the intestine In *carcinoma* of the stomach chronic ulceration of the intestine, stenosis of the large and the small intestine multiple anastomoses tu*berculous enteritis* regional ileitis carcinoma of the ileum or caecum and fecal fistulae there is usually an anemia which may be macrocytic and hyperchromic In many cases a mild hypochromic anemia occurs

Gaucher s Disease

The blood picture is variable Advanced cases may show a persistent leukopenia and at times a *mild* thrombocytopenia The red blood cells are usually normal but a mild anemia may be present in the late stages of the disease There are re

ports of a leuko-erythroblastic anemia and a pronounced leukocytosis with a shift to the left There may be anemia with nucleated cells, polychromatophilia basophilic stippling reticulocytosis and other evidence of active erythropoiesis

Glandular Fever

See Infectious Mononucleosis

Gonococcal Infections

There is mild to moderate neutrophilic leukocytosis, depending upon the site of infection

Gout

In the early stages there is a mild neutrophilic leukocytosis Sedimentation rate is elevated in severe attacks Hypercholesterolemia may be present.

Hand Schuller Christian Disease

There may be a moderate hypochromic anemia and late in the disease nucleated red cells and other evidence of active erythrogenesis may appear Leukopenia with a relative lymphocytosis may exist Some cases show a moderate thrombocytopenia

Hay Fever

See Allergy

Hemoconcentration

A sustained elevation of the erythrocyte count is present in a number of diseases including polycythemia vera and secondary polycythemia Hemoconcentration is entirely different from these conditions for it is an "acute erythrocytosis" characterized by a rapidly rising erythrocyte count, a decrease of total blood and plasma volume increased specific gravity of the blood and a sharp rise in hemoglobin values Hemoconcentration is caused by loss of plasma into the tissues and the acute erythrocytosis is the warning signal of impending disaster (shock) Significant hemoconcentration may be seen in acute poisonings, severe infections, burns, eclampsia hemorrhagic pancreatitis massive trauma to muscles prolonged intestinal manipulation mesenteric vascular occlusion freezing bile peritonitis, pulmonary edema intestinal strangulation acute peritonitis, therapeutic hyperthermia postoperative shock severe sunburn toxic jaundice diabetic coma and urticaria All types of shock, except that due to hemorrhage are preceded and accompanied by hemoconcentration Shock from hemorrhage is not accompanied by hemoconcentration because the blood becomes diluted (decreased hemoglobin and erythrocytes)

Hemoconcentration occurs many hours before signs of shock become evident and when a certain level of concentration is reached the blood pressure begins to fall rapidly and severe shock ensues The severity of shock parallels the degree of hemoconcentration Therefore hemoconcentration is a significant part of the development of circulatory failure in many clinical conditions It is important to remember that hemoconcentration occurs many hours before there is any alteration in the blood pressure and that careful study of the blood may give ample warning of the impending shock so that appropriate measures may be taken to prevent it

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mochromic Anemia from chronic blood loss is most often hypochromic and microcytic and there may be signs of regenerative erythropoiesis such as basophilic stippling reticulocytosis etc

Hemorrhagic Disease of the Newborn

The hematologic deviations from normal depend entirely upon the extent of bleeding There may be moderate leukocytosis and anemia The platelets are normal The coagulation and the bleeding times are prolonged The deficiency is one of prothrombin and the prothrombin time is increased

Hepatitis Acute Toxic

See Cirrhosis of the Liver

Hereditary Hemorrhagic Telangiectasia (Rendu Osler Weber Disease)

No typical hematologic picture is present After periods of bleeding whether acute or chronic the blood shows an anemia which is proportional to the amount lost

Histoplasmosis

Histoplasma capsulatum may be found in the large mononuclear cells of the peripheral blood or bone marrow There are usually moderate leukopenia and anemia

Hodgkin s Disease

Anemia is probably the most outstanding feature It is usually hypochromic with a gradual decrease in the total number of red cells as the disease progresses The blood picture may change to a leuko-erythroblastic type with immature leukocytes in the peripheral blood The leukocytes vary in number and as the disease becomes more advanced there is more likely to be a leukopenia In most case there is a moderate leukocytosis and occasionally there is a rather striking eosinophilia (15 per cent of the cases) The monocytes may be increased The platelets are usually normal

Hydatid Disease (Echinococcus)

As a rule the erythrocytes and the platelets are not affected and leukocytosis is a variable finding There is however a characteristic eosinophilia A similar type of picture is seen in infestations with bilharzia distoma coccidiosis granuloma and guinea worm

Hyperthyroidism

There is by no means a typical blood picture but in some patients there is a mild hypochromic anemia Neutropenia with a relative lymphocytosis may occur In some instances there may be an increase in the total number of lymphocytes

Hypothyroidism

It is fairly common to encounter a moderate hypochromic anemia No other hematologic changes of note are usually found On rare occasions lymphocytosis exists

Icterus Gravis Neonatorum

See Erythroblastosis of the Newborn

Idiopathic Hypochromic Anemia

The blood picture is one of microcytic hypochromic anemia In most

Hemoglobinuria Paroxysmal

See Paroxysmal Hemoglobinuria

Hemolytic Anemia Acquired (Chronic)

The blood picture closely resembles that of congenital hemolytic anemia except that the erythrocytes are not spherocytic they are more likely to be macrocytic with microcytosis seldom seen The reticulocyte count is often increased

Hemolytic Anemia Acute (Lederer Type)

There is a marked suddenly developing anemia with reticulocytosis and perhaps nucleated red cells There may be a leukemoid reaction which closely simulates a real leukemia During the leukopoietic phase there is flooding of the peripheral blood with immature granulocytes The icterus index is elevated with a positive indirect van den Bergh reaction

Hemolytic Anemia of the Newborn

In this type of anemia there is a rapid fall to an alarming degree in the erythrocyte level There may or may not be icterus A period of active erythropoiesis follows and showers the peripheral blood with nucleated red cells Leukocytosis varies from normal to moderate elevations

Hemolytic Jaundice Familial

The blood picture varies with the severity of the disease During remissions there are increased fragility of the red cells spherocytosis and reticulocytosis During more active hemolytic phases the red cell count drops rapidly when cell destruction exceeds marrow output The red cells appear small and deeply colored There is some variation in size and in shape of the red cells but the largest ones are in the normal range At about this stage a most remarkable reticulocytosis occurs and reaches high values There may be nucleated red cells The blood serum is icteric and the van den Bergh reaction is indirect The volume index is normal At all times the erythrocytes show increased fragility Leukocytosis is present and in some instances there is a leukemoid reaction In the chronic stage the blood picture is that of moderate anemia and leukocytosis slight reticulocytosis spherocytosis increased fragility of red cells and increase in the icterus index

Hemophilia

The degree of anemia depends on the amount of bleeding that has occurred If the blood loss has been extensive there will be a normocytic and hypochromic anemia The leukocyte count rises moderately following bleeding episodes There is a prolonged coagulation time so that the blood does not clot but there usually is no disturbance of cellular elements

Hemorrhage

If the hemorrhage is severe and rapid the red-cell count is not likely to fall significantly until several hours have elapsed The extent of hemorrhage governs the degree of anemia Nearly all cases show a moderate leukocytosis and this is more accentuated after severe hemorrhages The anemia is normocytic and nor

hemoglobin deficiency since the color index is much below normal However erythrocyte values may be normal or only slightly reduced The resulting anemia is microcytic and hypochromic The blood platelets and the leukocytes are normal

Jaundice Obstructive

See Cirrhosis of the Liver

Kala azar

The blood shows moderate anemia marked leukopenia with relative lymphocytosis and thrombocytopenia and prolonged bleeding and coagulation times There is no increase in serum proteins but the AG ratio may be reversed The organisms (Leishmania donovani) may be found in stained blood films or material from marrow aspiration

Lead Poisoning

The blood picture depends on the stage of the disease and the amount of exposure The acute cases are not likely to show any deviation from normal but in chronic plumbism there is a moderate anemia with the hemoglobin decreased considerably and the color index quite low The erythrocytes show some central pallor slight variations in size and in shape some polychromatophilia and usually basophilic stippling The reticulocytes are usually increased even when the cells are hypochromic The blood serum is slightly icteric The platelets are normal There may be a slight leukocytosis with some shift to the left

Lederer s Hemolytic Anemia

See Hemolytic Anemia Acute

Leishmaniasis (Kala azar) (Infantile Splenomegaly) (Tropical Ulcer)

Most cases show an anemia and a leukopenia with a relative lymphocytosis A marked monocytosis may also be present It is extremely difficult to find the causative organism in the peripheral blood

Leptospirosis

See Weil s Disease

Leukemia Acute

See Acute Leukemias

Leukemia Chronic

See Lymphatic Leukemia Myelogenous Leukemia Monocytic Leukemia

Leukocytosis Due to Drugs

Ingestion of the following drugs may produce a moderate degree of leukocytosis Quinine antipyrine phenacetin salicylates digitalis nucleic acid derivatives injected proteins (milk) turpentine and castor oil The sulfonamide drugs in addition to causing leukopenia may produce the most astounding degrees of neutrophilic leukocytosis (50 000 per cu mm., or more)

Liver Advanced Diseases of

Any far advanced disease of the liver which involves marked destruction of parenchymatous tissue may result in a macrocytic anemia because of inability of the organ to store the hematopoietic factor Such may occur in far advanced cirrhosis metastatic carcinoma multiple liver abscesses etc

cases the erythrocytes are not decreased as much as the hemoglobin and hypochromia is a marked feature The volume of the erythrocytes is low, and the average erythrocyte is much smaller than normal The blood smear reveals the presence of pale microcytes in large numbers The erythrocytes show a slight variation in size and in shape and occasionally basophilic stippling The blood platelets and the leukocytes are normal Achlorhydria is usually but not invariably present

Idiopathic Macrocytic Anemia of the Newborn

The blood picture is that of a macrocytic hyperchromic anemia with slight variation in shape and in size of erythrocytes However nucleated cells and reticulocytosis are rare until the phase of active erythropoiesis begins The fragility of the erythrocytes is normal Blood platelets are usually slightly reduced

Infantile Paralysis

See Poliomyelitis

Infantile Scurvy (Barlow s Disease)

There may be a moderate neutrophilic leukocytosis There is often a marked anemia with low hemoglobin low color index and occasionally immature red cells

Infants Anemia of (Prematurity)

Premature infants commonly have a rather marked anemia The hematologic picture is essentially that of a simple decrease in both erythrocytes and hemoglobin

Infectious Mononucleosis

This disease is characterized by a moderate to a marked leukocytosis with lymphocytes monocytes and atypical lymphocyte cells Erythrocytes hemoglobin and platelets are not affected The total leukocyte count may vary at different times and in different patients Most patients show a leukopenia sometime during the illness but even so the characteristic cells are present In the average case the mononucleosis cells constitute about 80 per cent of total cells This lasts for some time after the patient is clinically cured The heterophil antibody test is positive in at least 90 per cent of cases The Wassermann and the Kahn reactions may be temporarily positive during the active phase of the disease

Influenza

The typical picture is characterized by a neutrophilic leukopenia and relative lymphocytosis but the lymphocytes are not actually increased in number Occasionally however there is a mild leukocytosis Anemia is rare

Intestinal Obstruction

The blood picture is that of marked neutrophilic leukocytosis with a granulocytic shift to the left Hemoconcentration occurs if dehydration is marked this resulting in high red cell and hemoglobin values

Intestinal Parasitic Infestation

There are usually a microcytic hypochromic anemia and variable degrees of eosinophilia

Iron deficiency Anemia

The blood picture is typical of

Measles German

In general the blood picture is the same as that of measles The blood usually shows a neutropenia with a relative lymphocytosis Occasionally Turk cells plasma cells or eosinophils are present in fairly large numbers

Megakaryocytic Leukemia

The immature cell in this type of rare leukemia is the megakaryocyte Otherwise the hematologic findings are similar to those of other leukemias

Meningitis

A high neutrophilic leukocytosis is quite typical when the disease is caused by pyogenic organisms (meningococci streptococci staphylococci and pneumococci) In the chronic types of meningitis the count is much lower Anemia usually does not develop unless the disease is prolonged

Mikulicz s Syndrome

Some show normal blood while others show changes typical of chronic lymphatic leukemia

Monocytic Leukemia (Leukemic Reticulo endotheliosis) (Monocytoid Myelogenous Leukemia)

The typical findings include immature leukoblasts in the blood A variable degree of anemia develops and becomes progressively worse The predominant leukocyte is the immature monoblast and some more mature forms The percentage of monocytes immature and mature varies considerably, but when monoblasts are present the diagnosis is obvious There is a rather wide variation in the total leukocyte count (from 5 000 to 240 000) The blood platelets are decreased so that bleeding is a common complication

Multiple Myeloma (Plasmacytoma) (Plasmoma) (Kahler s Disease)

A hypochromic anemia is present in nearly every case It is usually progressive There are usually a leukocytosis with increased lymphocytes a few Turk cells and scattered myelocytes and there may be an occasional myeloblast In some cases the leukocytes may be of the plasma cell type A leuko-erythroblastic type of blood picture is not uncommon Because of high protein values the red cells may show a tendency to auto agglutination The aspirated marrow may show typical myeloma cells

Mumps

There is usually a moderate leukopenia with a relative lymphocytosis Also there may be a marked increase in monocytes in the later stages

Mycotic Diseases

There is usually no change in the leukocyte picture or there may be a mild leukopenia The degree of anemia depends on the extent and the duration of the illness

Myelogenous Leukemia Chronic

The blood findings are characteristic The degree of anemia is variable but becomes worse as the disease progresses When the leukemic process encroaches on erythropoietic cen

Liver, Cirrhosis of

See Cirrhosis of the Liver

Ludwig's Angina

See Angina, Ludwig's

Lupus Erythematosus, Disseminated

There is no typical blood picture In the advanced stage there may be a rather marked anemia with low color index A leukopenia may be present or there may be a slight leukocytosis with a moderate shift to the left Eosinophilia may occur on rare occasions as in other skin disorders

Lymphatic Leukemia, Chronic

The blood picture shows a characteristic leukocytosis (100 000 more or less) with the predominating cells being lymphocytes small large and immature Most of the lymphocytes appear fairly mature but some are immature with nucleoli Basket cells and smudge cells are numerous The blood platelets are reduced at times causing prolonged bleeding time and poor clot retraction The associated anemia may be a simple hypochromic type

Lymphocytic Choriomeningitis

There are no characteristic blood findings

Malaria

The characteristic findings are parasites in the red blood cells leukopenia and anemia All cases do not show a leukopenia During the actual paroxysms there is a leukocytosis which is later followed by a leukopenia In some of the erythrocytes there may be Schuffner's dots (fine acidophilic granules) or Maurer's dots (rather coarse basophilic granules) Abnormal amounts of pigment appear in the cytoplasm of some of the leukocytes In the later stages and more chronic forms of malaria there is an increase in the monocytes and the lymphocytes In chronic cases anemia is a constant finding It is usually microcytic and hypochromic The platelets are usually not affected The red blood cells containing the tertian parasites are quite enlarged and pale

Malignant Neutropenia (Agranulocytosis)

The blood picture is characteristic There is an absence of neutrophilic leukocytes in the peripheral blood and there is a decrease in lymphocytes and in monocytes The disease may reach the stage where the total leukocyte count will be only a few hundred cells per cubic millimeter The red cells are usually not affected but a profound anemia can develop if the disease is due to a drug having a hemolytic action

Some people have what is termed chronic neutropenia with a leukocyte count of from 3000 to 4000 per cu mm

Measles

Early in the disease there is a leukocytosis with a shift to the left This is followed later by a neutropenia Turk cells may be present Occasionally there are a moderate eosinophilia and relative lymphocytosis On rare occasions plasma cells are present in the peripheral blood Even when there is a neutropenia the granulocytes are of the immature types

Oroya Fever (Bartonella Fever)

A very severe hemolytic anemia develops fairly early The anemia is frequently a hyperchromic macrocytic type with variation in size and in shape of the erythrocytes with polychromatophilia nucleated cells and reticulocytosis The characteristic rod shaped bacilli can usually be found in the blood smear

Osteomyelitis

In osteomyelitis the most common finding is a high leukocyte count with a marked shift to the left An eosinophilia may be present Anemia rarely occurs Leukemoid reactions are more prone to develop in children

Osteosclerosis (Marble bone Disease) (Disease of Albers Schonberg)

In most cases the blood picture shows only a mild anemia However the leukocytic picture may resemble that of myeloid leukemia with the anemia changing to an erythroblastic type

Otitis Media

There is usually a moderate neutrophilic leukocytosis If mastoiditis develops the leukocyte count rises sharply Anemia rarely occurs except in complications

Ovalocytosis

The blood shows no abnormality except that some of the erythrocytes are oval in shape This is a familial abnormality and is not related to sickle cell anemia

Pancreatitis Acute

There is usually a moderate to a severe neutrophilic leukocytosis

Parasites Intestinal

There is nearly always a moderate to a marked eosinophilia with varying degrees of anemia based upon the duration and the extent of infestation

Paroxysmal Hemoglobinuria

Since this condition is a hemolytic anemia with excessive red-cell destruction there is an anemia which is usually normocytic and normochromic The plasma is usually icteric Following rapid destruction of the erythrocytes there is a compensatory period of regeneration which is characterized by nucleated erythrocytes reticulocytosis and sometimes basophilic stippling Usually there is a neutropenia just after the chill followed later by a definite leukocytosis Blood pigment in the form of hemoglobin is present in the blood plasma and the urine A few cases may develop a hypochromic anemia of mild degree

Pellagra

A macrocytic hyperchromic anemia may be present but it is not as severe as that seen in pernicious anemia Not all cases develop anemia and some may show a mild hypochromic and microcytic type

Penicillin Administration of

So far as is known no characteristic blood changes are produced by the administration of penicillin

Peptic Ulcer Perforated

There is no anemia unless the pa

ters the peripheral blood is likely to show nucleated erythrocytes poly chromatophilia variation in size and in shape of the cells and some baso philic stippling The characteristic finding is the presence of immature cells of the granulocytic series Myeloblasts are few but myelocytes juveniles and bands are numerous Many of the myelocytes show baso philic or eosinophilic granules and the presence of basophilic myelocytes nearly always indicates myelogenous leukemia The total leukocyte count is usually elevated but it may be lower than normal (aleukemic phase) In chronic myeloid leukemia at least 95 per cent of the leukocytes are of the granulocytic series Blood platelets are decreased during some stage of the disease so that the bleeding time is prolonged and clot retraction is poor

Myelosclerosis

See Osteosclerosis

Myxedema (Hypothyroidism)

Several types of anemia may occur but a normochromic anemia is most common Other types include the microcytic hypochromic and the macrocytic Oftentimes a lymphocytosis occurs

Neoplasms

The blood picture is not characteristic but the blood changes depend upon the location and the type of malignancy In nearly all malignancies there is anemia and those of the stomach and the upper gastro intestinal tract are likely to produce a macrocytic anemia especially when extensive liver metastases are present Anemia may also be caused by extensive involvement of the bone marrow The leukocyte count is usually normal until complications develop These are usually secondary infections and result in a moderate leukocytosis Extensive bone marrow metastases produce anemia showers of nucleated erythrocytes and frequently an associated leukemoid reaction

An obscure anemia characterized by large numbers of nucleated erythrocytes and a leukemoid reaction in a person in the cancer age may indicate marrow metastases from some unseen malignancy

Nephritis

The change most commonly seen is an anemia in either acute nephritis or the chronic forms of it The degree of anemia varies and it may be of the normocytic the microcytic hypochromic or the macrocytic types In general the degree of anemia seems to parallel nitrogen retention A slight leukocytosis may be present at any stage of the disease

Niemann Pick Disease

There are usually a moderate hypochromic anemia and a slight leukocytosis However a leukopenia may be present Monocytes lymphocytes and granulocytes may show the characteristic lipoid vacuoles in their cytoplasm

Nutritional Anemia of Infants

The blood picture is characterized by a hypochromic microcytic anemia In a few cases there is a marked fall in the hemoglobin with a more or less normal erythrocyte count

there is a moderate hypochromic anemia accompanied by achlorhydria

Pneumonia Lobar (Pneumococcal)

The blood picture is quite constant in most cases and is characterized by a very marked neutrophilic leukocytosis Many of the granular leukocytes are immature types so that it is not uncommon to find a few myelocytes in the blood smear An occasional patient shows a leukopenia which may be a bad prognostic sign but there is still a marked shift to the left There is usually no anemia except in prolonged cases when a mild hypochromic anemia is likely to develop In the early stages eosinophils disappear from the blood After the crisis has passed the leukocyte count gradually returns to normal so if the count should rise again during this period it is likely that some complication has developed

Pneumonia Virus (Pneumonia Atypical)

Leukocyte count nearly always normal perhaps slightly elevated if secondary infection takes place Sedimentation rate moderately elevated

Poisons

In certain cases of poisoning very peculiar blood pictures may be seen Myeloid reactions have been seen in mercury and in mustard gas poisoning Bee stings have caused leukemoid reactions with high total white-cell counts A large number of chemicals produce bizarre blood pictures Leukopenia and even agranulocytosis can be caused by benzene amidopyrine arsphenamine dinitrophenol gold salts gasoline fumes arsenic radioactive substances and x rays Acetanilid may produce a methemoglobinemia and an eosinophilia The sulfonamide group of chemicals may produce leukopenia hemolytic anemia or thrombocytopenia Phenylhydrazine potassium chlorate and benzedrine can produce hemolytic anemia Arseniuretted hydrogen can cause a very severe anemia and produce death in a few hours Saponin ricin and some snake venoms have a definite hemolytic action Cobra venom has produced a megaloblastic reaction of the bone marrow The eating of certain beans in Italy (*Vicia face*) or inhalation of the pollen from the plants can cause a hemolytic anemia Extreme leukocytosis (140 000 cu mm) may occur during the administration of sulfonamide drugs Sedormid has been incriminated in the production of thrombocytopenic purpura

Poliomyelitis (Infantile Paralysis)

In the acute and the early stages there is usually a moderate leukocytosis with an increase in lymphoid cells In some patients the blood shows no significant changes

Polycythemia Hypertonica (Geisbock s Disease)

The blood picture is the same as that in polycythemia vera

Polycythemia Secondary

The blood picture in certain diseases is almost the same as in true polycythemia These diseases are con

tient has previously bled from the ulcer and then the anemia is in proportion to the blood loss Almost all cases show a marked neutrophilic leukocytosis soon after the perforation In rare cases there is a marked leukopenia but the cells present are predominantly young or immature granulocytes A patient with perforated ulcer can have a leukopenia from overwhelming peritoneal shock

Periarteritis Nodosa

The blood picture seems to be quite variable except that most cases have a moderate neutrophilic leukocytosis and a progressive anemia Eosinophilia is found only in about 15 per cent of the cases The anemia parallels the stage of the disease and is quite marked in the advanced stage Cases with marked pulmonary symptoms (asthmatic type) are likely to show extreme degrees of eosinophilia

Peritonitis, Acute, Generalized

There is a moderate to a severe neutrophilic leukocytosis depending upon the severity and the duration of the disease In overwhelming infections there may be a period of leukopenia but with neutrophils showing a marked left shift This occurs during the period of mobilization of the leukocytes to the infected areas

Pernicious Anemia

The blood picture varies with the stage of the disease During a severe relapse the red cells may reach a very low level and the color index is above one The red cells show a marked variation in size and in shape show polychromatophilia basophilic stippling megaloblasts and other nucleated cells Many of the red cells are macrocytes but microcytes are also present The reticulocytes usually are quite low until active regeneration begins and then there is marked reticulocytosis During active liver therapy there is a marked reticulocytosis as the blood returns to normal There may be a leukopenia in the period of relapse with a relative lymphocytosis Some smears show hypersegmentation of the granulocytes Eosinophilia may be quite marked during the period of active therapy

Pertussis

See Whooping Cough

Plague Bubonic

See Bubonic Plague

Plasma Cell Leukemia

This disease does not differ from other types of leukemia except that the predominating leukocytes have the characteristics of plasma cells Only a few cases have been reported See Multiple Myeloma

Pleurisy

There is usually a neutrophilic leukocytosis the degree depending upon the type of infecting organism and the amount of pleural tissue involved There is an associated anemia if the process is prolonged In tuberculous pleurisy with effusion there is very little change in the cell count

Plummer Vinson Syndrome

Not all cases have hematologic changes In most instances however

Purpura Nonthrombocytopenic (Purpura Simplex) (Henoch's Purpura) (Schonlein's Disease) (Allergic Purpura) (Purpura Fulminans)

In this disorder there is an anemia parallel to the amount of blood lost. A moderate leukocytosis usually exists and the blood platelets are normal in number. The tourniquet test is positive. The defect seems to be a weakness in the capillary walls.

Pyogenic Infections

As a rule, all acute pyogenic infections give rise to a blood picture common to the entire group. These infections include subcutaneous abscess, lung abscess, abscess of the brain, abscess of liver, kidneys and spleen, subdiaphragmatic abscess, acute salpingitis, acute cholecystitis, acute and chronic pyelonephritis, acute cystitis, acute mastitis, acute cholangitis, acute tonsillitis, pharyngitis, retropharyngeal abscess and bronchitis, acute mediastinitis and pericarditis, multiple abscesses of the peritoneal cavity, acute arthritis, acute sinusitis, pleurisy, suppurative phlebitis and osteomyelitis. All are characterized by a marked leukocytosis with a shift to the left. There is no anemia unless the disease is prolonged or is complicated by other features.

Radiation Effects

See Aplastic Anemia, Secondary.

Radium Poisoning

There may be variable degrees of leukopenia, anemia and thrombocytopenia depending upon the extent and the duration of exposure to radium.

Rat Bite Fever

The organisms are found frequently in the peripheral blood. The blood should be examined by darkfield illumination or special stains used on fixed blood smears. (See Plate 32.)

Relapsing Fever

There is usually a neutrophilic leukocytosis with a left shift. The spirochetes sometimes are seen on stained blood films. Serologic tests are positive in about 20 per cent of cases. (See Plate 32.)

Rheumatic Fever

There is a moderate neutrophilic leukocytosis early in the disease with increased cells of the immature granulocytic series. Occasionally there is a moderate eosinophilia, which is even more likely to occur if there is chorea (acute type). Ordinarily a mild anemia develops. This is usually of the microcytic hypochromic type.

Rocky Mountain Spotted Fever

Nearly all cases have some degree of neutrophilic leukocytosis and some increase in monocytes.

Roseola Infantum

See Exanthem Subitum.

Rubella

See German Measles.

Salmonella Infections

There is usually a leukopenia of mild degree that lasts from one to three weeks with leukocytosis in the late stages and a mild anemia throughout the illness.

genital heart disease (cyanotic type) Ayerza's disease extreme pulmonary emphysema pituitary basophilism (Cushing's syndrome) Huntington's chorea (rarely) encephalitis lethargica (rarely) thrombosis of splenic vein (rarely) visceral syphilis (rarely) chronic carbon monoxide poisoning myocardial disease massive atelectasis stenosis of the bronchial tree pneumothorax chronic pulmonary disease, and poisoning from such chemicals as benzene nitrobenzene aniline arsenic, phosphorus acetanilid and antipyrine People living at high altitudes develop a compensatory polycythemia The blood picture shows a marked increase in erythrocytes and in hemoglobin but the color index is frequently below one The picture may at times be the same as true polycythemia

Polycythemia Vera

The hematologic picture is the basis for the diagnosis in this disease The blood is grossly dark thick sticky and viscous The erythrocytes are markedly increased in number, and hemoglobin values are high The blood platelets are increased At any time during the disease the white cell picture may simulate that of myelogenous leukemia with a high leukocyte count and numbers of immature granulocytes When the peripheral blood depicts a leukemoid reaction and there is evidence of extreme erythrogenesis the picture has been called erythroleukemia It is well known that cases of true polycythemia may terminate as myelogenous leukemia The total blood volume as well as the total cell volume, is increased

Polymyositis, Acute

In some instances it is necessary to differentiate this condition from trichina infection In polymyositis the eosinophilia develops early and then subsides, whereas in trichina infection there is a marked persistent eosinophilia A mild neutrophilic leukocytosis is usually present in both diseases Anemia is rare

Pregnancy

There is a variable degree of leukocytosis during pregnancy However, if macrocytic anemia develops there is likely to be neutropenia with a relative lymphocytosis The blood platelets are normal The usual anemia is hypochromic and microcytic However in rare instances a hyperchromic macrocytic anemia simulating pernicious anemia may develop

Purpura Essential Thrombocytopenic (Idiopathic Thrombocytopenic Purpura)

The characteristic picture is that of an extreme decrease in the blood platelets some of those present being of giant size and bizarre in form The platelets may be absent in the blood smear The clot does not retract is poorly formed and is fragile The bleeding time is prolonged The number of red cells depends on the amount of bleeding The tourniquet test is positive A slight to a moderate leukocytosis may exist The chief defect is a deficiency of blood platelets

Simmonds's Disease (Hypopituitarism)

A mild hypochromic anemia frequently occurs The leukocytes may be normal but a slight lymphocytosis has been reported

Smallpox

In the early stages there is a neutropenia but later there is a leukocytosis which is most marked during the stage of pustule formation and secondary infection In the late stages the leukocytosis is caused by an increase in lymphocytes and in monocytes

Spirochetosis Icterohaemorrhagica

See Weil's Disease

Sprue

During the early stages of the disease the blood usually shows a very mild hypochromic microcytic anemia As the disease progresses there may be a change to a macrocytic type similar to that of true pernicious anemia In the advanced case the erythrocytes are decreased in number and show variation in size and in shape and present also are macrocytosis polychromatophilia and an occasional nucleated erythrocyte However reticulocytes are usually low until treatment has begun There may be neutropenia

Staphylococcal *Infections* (Furuncle Carbuncle Staphylococcal Bacteriemia Staphylococcal Pneumonia Etc)

There is practically always a moderate to an extreme neutrophilic leukocytosis with a marked left shift

Steatorrhea Idiopathic

See Celiac Disease

Stomach *Carcinoma of*

There is usually a variable degree of anemia which is frequently macrocytic in type and indistinguishable from the blood picture of pernicious anemia Also a mild to a moderate neutrophilic leukocytosis may be present

Streptococcal Infection

There is usually a mild to a moderate leukocytosis with a neutrophilic left shift In overwhelming infections there may be a leukopenia with left shift in neutrophils

Sulfonamide Drugs Administration of

An occasional patient receiving sulfonamide drugs may develop acute hemolytic anemia another may develop neutropenia still another may show leukemoid reactions because of bone marrow stimulation and a fourth blood complication may be thrombocytopenic purpura

Syphilis

The blood picture varies with the stage of the disease There may be a microcytic hypochromic anemia in the secondary stage as well as a moderate lymphocytosis Antisyphilitic therapy may occasionally produce secondary aplastic anemia Tertiary syphilis is accompanied frequently by an anemia that is even more marked if cardiovascular manifestations are present Leukopenia with a relative lymphocytosis is common in the tertiary stage. Occasionally there

Sarcoidosis (Boeck s Sarcoid)

There may be a slight leukopenia or a normal leukocyte count The monocytes are usually increased and there is eosinophilia of slight or moderate degree Usually there is a mild hypochromic microcytic anemia The plasma proteins are increased and the AG ratio is frequently reversed.

Scarlet Fever

There are a rather marked neutrophilic leukocytosis and a mild eosinophilia in the beginning of the disease These conditions persist throughout the illness A low eosinophil count is supposed to indicate a bad prognosis

Scurvy (Vitamin C Deficiency)

The blood picture is not altered in all cases but an anemia of the hypochromic microcytic type is common In rare instances there is a leukocytosis with a few immature granulocytes Leukopenia sometimes occurs The platelets usually are not altered The bleeding and the clotting times are normal The hematologic picture in infantile curvy is different in that infants are more likely to show a more profound anemia and more evidence of regeneration in the peripheral blood The vitamin-C content of the blood is low

Septicemia Streptococcal

There are usually a rapidly progressing anemia and a mild to a moderate leukocytosis with neutrophilic left shift In overwhelming infections there is leukopenia with a left shift

Serum Sickness

There is usually a moderate leukocytosis Eosinophilia usually occurs after venom injections After the intravenous injection of typhoid vaccine sufficient to produce a marked reaction there is a marked neutropenia and the blood platelets disappear temporarily from the blood After injection of tuberculin there may be eosinophilia

Shock

See Hemoconcentration

Sickle Cell Anemia

The blood picture of this hemolytic anemia is characterized by the presence of bizarre crescent shaped or sickle shaped red corpuscles They average from 10 to 20 microns in length and from 2 to 4 microns in width There may be only the sickling tendency without anemia but during the acute phase there are a profound anemia low hemoglobin and color index and a moderate to a marked leukocytosis During the phase of active erythrogenesis the peripheral blood contains many nucleated red corpuscles and reticulocytes and may show a leukemoid reaction During chronic phases there may be only a mild anemia and the characteristic sickling The blood serum is icteric and bile pigments are present in the urine

Silicosis

There is a slight leukocytosis in the beginning of the disease with a tendency toward leukopenia in the later stages There is also an iron deficiency anemia which is usually progressive

whereas a lymphocytosis is associated with healing Children are likely to have a higher monocytosis than adults but it bears no relation to the severity of the process

Tularemia

The blood picture is by no means typical but most patients have a mild neutrophilic leukocytosis

Typhoid and Paratyphoid Fever

There is usually a leukopenia with a relative lymphocytosis and mono cytosis Neutrophilic leukocytosis de velops when there is a complication such as perforation of the intestine or bronchopneumonia Usually there is a microcytic hypochromic anemia which in some instances may be se vere A rapid anemia develops if there is hemorrhage from the intestinal tract

Typhus Fever

This disease is characterized by a neutropenia with a relative lymphocytosis and the few granulocytes present may be quite immature Anemia is unusual There may be a mod erate increase in monocytes and in lymphocytes in the late stages

Undulant Fever

In prolonged cases there is a mod erate microcytic hypochromic ane mia The leukocytes may be normal or decreased at the expense of the neutrophils with a relative lymphocytosis Occasionally there may be a monocytosis

Varicella

See Chickenpox

Virus Diseases

As a rule the entire group of virus diseases is characterized by leuko penia in the early stages but if fol lowed by secondary invasion by bac teria leukocytosis may be present

Virus Pneumonia

See Pneumonia Virus

Vitamin C Deficiency

See Scurvy

von Jaksch s Anemia (Anemia Pseudoleukemia Infantum)

The typical blood picture is one of hemolytic anemia and a leukemoid reaction The anemia develops rapidly The stage of erythrogenesis be gins with the appearance of erythroblasts and results in a marked eryth roblastemia Many of the red cells show basophilic stippling The plate lets are normal or slightly decreased The icterus index is increased by an indirect van den Bergh reaction There is usually a high leukocyte count with a shift to the left At times it may simulate myeloid leukemia with the presence of a rare myelo blast a few myelocytes and other im mature cells

Weil s Disease (Leptospirosis) (Icterohaemorrhagica)

There is a moderate to a marked leukocytosis present from the onset with a neutrophilic left shift The icterus index is high and the van den Bergh reaction is usually indirect Anemia is more marked as the dis ease progresses There are organisms in the blood in the early stages and they can best be demonstrated by in

is a slight monocytosis Congenital syphilis is nearly always characterized by hypochromic anemia and lymphocytosis Also, erythroblastic reactions are not uncommon in the congenital type The blood changes parallel the stage of activity, and the findings depend on the stage and the severity of the infection

Telangiectasia, Hereditary Hemorrhagic

See Hereditary Hemorrhagic Telangiectasia

Tetanus

There is no typical peripheral blood picture in this disease

Thrombo angiitis Obliterans

Many patients with this disease show a moderate neutrophilic leukocytosis and also some degree of erythrocytosis or secondary polycythemia

Thrombocytopenic Purpura

See Purpura Essential Thrombocytopenic

Thrombophlebitis

The blood picture depends upon the extent and the severity of the process and whether suppuration is present As a rule the leukocytes are elevated the extent depending on the activity of the process Anemia is not seen unless the disorder is complicated by bacterial infection with septicemia

Trichiniasis

There is nearly always a very marked eosinophilia There is no alteration in erythrocytes platelets or hemoglobin A slight leukocytosis occurs in most cases during the acute phase, and in some instances the entire white-cell increase may be caused by the increased eosinophils

Trypanosomiasis (Sleeping Sickness)

There are organisms in the blood which may be demonstrated by examining a drop of fresh blood There are no cellular changes of significance, except hypochromic anemia in cases of long standing

Tuberculosis

The blood picture is not typical in this disease but certain features may give some indication of the activity of the process In acute miliary tuberculosis there is a moderate progressive hypochromic anemia which usually persists as long as the patient lives This form of tuberculosis is frequently accompanied by a leukopenia

Acute pulmonary tuberculosis is usually characterized by a moderate hypochromic anemia and a leukopenia but in some cases a slight leukocytosis occurs when there is marked secondary infection

Chronic pulmonary tuberculosis is often accompanied by a microcytic hypochromic anemia, especially in cases when the lesion is active and progressive The leukocyte count and the cell types vary with the activity of the process If the process is septic there is leukocytosis The hyperplastic type shows a slightly elevated leukocyte count and an increase in monocytes or lymphocytes according to the trend of the process An increase in monocytes usually denotes activity

whereas a lymphocytosis is associated with healing Children are likely to have a higher monocytosis than adults but it bears no relation to the severity of the process

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See Chickenpox

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See Pneumonia Virus

Vitamin C Deficiency

See Scurvy

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jecting blood into a guinea pig by the intraperitoneal route

Whooping Cough

Early in the disease there may be a leukopenia but later the characteristic blood picture is one of extreme lymphocytosis the lymphocytes comprising from 65 to 75 per cent of the total cells, to such an extent that the blood picture may simulate chronic lymphatic leukemia When complicated by bronchopneumonia there may be a granulocytic response with immature neutrophils present in considerable numbers

Yellow Fever

There is a leukopenia in the early stages It reaches its lowest point about the fifth or the sixth day the blood remaining normal throughout the remainder of the illness except for an anemia in the late stages

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